Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
February 7, 2024

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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 ensure 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.

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 preferred with clinical criteria, are 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:

Accumulation Edit
Brand Limit Switchover
Dispense As Written Override
Early Refill
Ingredient Duplication
Maintenance Supply Opt Out
Maximum Unit/Max Cost Limitations
Short Acting Opioid Naïve Override
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-10 code(s) may be used. Use of ICD-10 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic, OTC 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, OTC 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, OTC 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, OTC, 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 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

Antihyperlipidemic Agents

Appropriate Diagnosis

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

Prior Treatment Trials

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

- For Zetia®, if prior usage requirements have not been met, approval may be obtained for adjunctive therapy to a current lipid lowering drug.

- For Praluent®, Repatha®, Nexletol®, or Nexlizet®, 12 weeks of prior therapy with at least 2 maximally tolerated doses of statins is required. If prior usage requirements for these agents have not been met, approval may be obtained for adjunctive therapy to a maximally tolerated statin (or a statin or ezetimibe for patients with a diagnosis of familial hypercholesterolemia).

- For Juxtapid® or Evkeeza®, 12 weeks of prior therapy with at least 2 maximally tolerated doses of statins is required. If prior usage requirements for these agents have not been met, approval may be obtained for adjunctive therapy to a maximally tolerated statin, ezetimibe, and a PCSK9 inhibitor for patients (≥12 years of age) with a diagnosis of homozygous familial hypercholesterolemia.

Stable Therapy

- Approval for the oral products 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

- For oral agents, approval may be given for up to 6 months for initial request and up to 12 months for renewal requests.

- For Praluent®, Repatha®, Nexletol®, Nexlizet®, Juxtapid®, or Evkeeza®, approval may only be given for 6 months and renewal requests are contingent on sufficient decrease in LDL from onset of initiation of therapy.

Electronic Prior Authorization (PA)

- Antilipemic agents are included in the electronic PA program.

Verbal PA Requests

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

Cardiac 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 cardiac 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.

- To meet these prior usage requirements, drugs within this specific classification must be judged against others in the same class (AHFS specific).

    - For example, to qualify for a non-preferred cardiotonic, the patient must have met prior usage requirements of 30-day treatment trials with two other preferred cardiotonic agents, either generic, OTC or brand.

    - For Ranexa®, in lieu of prior usage requirements, approval may be obtained for adjunctive therapy to a current antianginal drug.

    - For Corlanor®, previous beta-blocker usage or contraindication to beta-blocker therapy is required.

    - For Entresto®, one (1) prior therapy with either an angiotensin receptor blocker or ace inhibitor is acceptable.

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 (PA)

- Cardiac agents are included in the electronic PA program.

Verbal PA Requests

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

Oral Anticoagulants

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 one prescribed and preferred oral anticoagulant in this class, either generic, OTC, or brand, within the past six months, or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given to 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)

- Oral anticoagulants are included in the electronic PA program.

Verbal PA Requests

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

Platelet-Aggregation Inhibitors

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 2 prescribed and preferred platelet-aggregation inhibitors 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.

- For Verquvo®, the patient must be symptomatic despite receiving standard of care therapy with an ACEI, ARB, or ARNI in combination with a β-blocker (carvedilol, metoprolol succinate or bisoprolol) or have a documented contraindication, allergy or intolerance to the use of these agents.

Stable Therapy

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

Medical Justification

- Acceptable medical justification consists of specific clinical diagnoses for 1st line treatment by certain branded products in lieu of prior usage, allergy, contraindication or intolerance to the use of aspirin, cilostazol, ticlopidine and dipyridamole.

- Clinical literature and guidelines support the use of Aggrenox®, Brilinta®, and Effient® for specific 1st line indications; these indications include acute coronary syndrome, acute myocardial infarction (NSTEMI and STEMI), peripheral arterial occlusive disease (PAD, PVD), transient ischemia or ischemic stroke due to thrombosis/embolism, and percutaneous coronary interventions (balloon angioplasty, laser angioplasty, intra-coronary stents, other catheter devices treating coronary atherosclerosis).

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Platelet-aggregation inhibitors are included in the electronic PA program.

Verbal PA Requests

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

Antidepressants

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 antidepressant 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 to 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)

- Antidepressants are included in the electronic PA program.

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

February 7, 2024
1:00 p.m. – 3:00 p.m.

1. Opening remarks…….Chair
2. Approval of November 8, 2023 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 reviews…….University of Massachusetts Clinical Pharmacy Services
   - Anticoagulants, Oral – AHFS 201204
   - Platelet-aggregation Inhibitors – AHFS 201218
   - Vasodilating Agents, Miscellaneous – AHFS 241292
   - Antiarrhythmic Agents – AHFS 240404
   - Cardiotonic Agents – AHFS 240408
   - Cardiac Drugs, Miscellaneous – AHFS 240492
   - Bile Acid Sequestrants – AHFS 240604
   - Cholesterol Absorption Inhibitors – AHFS 240605
   - Fibric Acid Derivatives – AHFS 240606
   - HMG-CoA Reductase Inhibitors – AHFS 240608
   - Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors – AHFS 240624
   - Antilipemic Agents, Miscellaneous – AHFS 240692
   - Nitrites and Nitrates – AHFS 241208
   - Renin-Angiotensin-Aldosterone System Inhibitors, Misc – AHFS 243292
   - Antidepressants – AHFS 281604
6. New drug review …….….University of Massachusetts Clinical Pharmacy Services
   - Veozah® (fezolinetant)
7. New business .....Alabama Medicaid
   - Antidiabetic Criteria Discussion
8. Results of voting announced……..…….....……Chair
9. Next meeting dates
   - May 8, 2024
   - August 7, 2024
   - November 6, 2024
10. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anticoagulants, Oral
AHFS Class 201204
February 7, 2024

I. Overview

Apixaban (Eliquis®), dabigatran etexilate mesylate (Pradaxa®), edoxaban (Savaysa®), rivaroxaban (Xarelto®), and warfarin are oral anticoagulants approved by the Food and Drug Administration (FDA) for the various cardiovascular indications outlined in Table 3.[1-5] Warfarin has been the principle oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy in all of its FDA-approved indications.[6-8] Apixaban and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor (DTI). All are novel oral anticoagulants that are approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) and for treatment and reduction in the risk of recurrence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have previously been treated.[1-4] These agents also have a variety of specific additional cardiovascular indications. Rivaroxaban received an expanded indication for two pediatric indications including for treatment of venous thromboembolism and reduction in the risk of recurrent venous thromboembolism in pediatric patients birth to 18 years of age and for thromboprophylaxis in pediatric patients two years of age and older with congenital heart disease after the Fontan procedure.[4] Dabigatran has gained indications in pediatric patients as young as three months of age with approval of the oral pellet dosage form.[2]

Warfarin is a vitamin K antagonist (VKA) that works by interfering with the synthesis of vitamin K dependent clotting factors and anticoagulant proteins C and S. Specifically, warfarin inhibits the vitamin K epoxide reductase enzyme complex, resulting in the blockade of the regeneration of vitamin K1 epoxide.[5-8] Conversely, the non-vitamin K oral anticoagulants target a single enzyme involved in the coagulation cascade. Dabigatran etexilate mesylate is a prodrug that is converted to dabigatran, a potent, competitive inhibitor of thrombin. As a DTI, dabigatran inhibits the conversion of fibrinogen into fibrin; thereby inhibiting the development of a thrombus. Both free and fibrin-bound thrombin and thrombin-induced platelet aggregation are inhibited by dabigatran etexilate mesylate.[2,7,8] Apixaban, edoxaban, and rivaroxaban selectively inhibit factor Xa, thereby preventing the generation of thrombin and ultimately preventing platelet activation and the formation of fibrin clots.[1,3,4,7,8]

The oral anticoagulants included in this review are listed in Table 1. This review encompasses only oral dosage forms and strengths within the AHFS class. Dabigatran and warfarin are available in generic formulations. This class was last reviewed in February 2022.

Table 1. Oral Anticoagulants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Apixaban	tablet	Eliquis®	Eliquis®
Dabigatran	capsule, pellet pack	Pradaxa®*	Pradaxa®*
Edoxaban	tablet	Savaysa®	none
Rivaroxaban	suspension, tablet	Xarelto®	Xarelto®
Warfarin	tablet	N/A	warfarin

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Oral Anticoagulants

Clinical Guideline	Recommendations
American College of Chest Physicians:	Management of anticoagulant therapy • For outpatients, vitamin K antagonist (VKA) therapy with warfarin 10 mg/day

Clinical Guideline	Recommendations
Antithrombotic Therapy and Prevention of Thrombosis, 9th edition (2012)[6]	for the first two days, followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose is suggested. • Routine use of pharmacogenetic testing for guiding doses of VKA therapy is not recommended. • For acute venous thromboembolism (VTE), it is suggested that VKA therapy be started on day one or two of low molecular weight heparin (LMWH) or low dose unfractionated heparin (UFH) therapy rather than waiting for several days to start. • For VKA therapy with stable INRs, INR testing frequency of up to 12 weeks is suggested rather than every four weeks. • For patients receiving previously stable VKA therapy who present with a single out-of-range INR ≤0.5 below or above therapeutic, it is suggested to continue the current dose and test the INR within one to two weeks. • For patients receiving stable VKA therapy presenting with a single subtherapeutic INR value, routine administering of bridging heparin is not recommended. • Routine use of vitamin K supplementation is suggested against with VKA therapy. • For patients receiving VKA therapy who are motivated and can demonstrate competency in self-management strategies, it is suggested that patient self-management be utilized rather than usual outpatient INR monitoring. • For maintenance VKA dosing, it is suggested that validated decision support tools be utilized rather than no decision support. • Concomitant use of nonsteroidal anti-inflammatory drugs and certain antibiotics should be avoided in patients receiving VKA therapy. • Concomitant use of platelet inhibitors should be avoided in patients receiving VKA therapy, except in situations where benefit is known or is highly likely to be greater than harm from bleeding. • With VKA therapy, a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended rather than a lower (<2.0) or higher (range, 3.0 to 5.0) range. • In patients with antiphospholipid syndrome with previous arterial or VTE, VKA therapy should be titrated to a moderate intensity INR (range, 2.0 to 3.0) rather than higher intensity (range, 3.0 to 4.5). • For discontinuations of VKA therapy, it is suggested that discontinuation be done abruptly rather than gradual tapering of the dose. • For initiation of intravenous (IV) UFH, the initial bolus and rate of continuous infusion should be weight adjusted or fixed-dose rather than alternative regimens. • In outpatients with VTE receiving subcutaneous (SC) UFH, dosing should be weight-based without monitoring rather than fixed or weight-adjusted dosing with monitoring. • A reduction in therapeutic LMWH dose is suggested in patients with severe renal insufficiency rather than using standard doses. • In patients with VTE and body weight >100 kg, the treatment dose of fondaparinux should be increased from 7.5 to 10 mg/day SC. • For INRs between 4.5 and 10.0 with VKA therapy and no evidence of bleeding, routine use of vitamin K is not recommended. • For INRs >10.0 with VKA therapy and no evidence of bleeding, it is suggested that oral vitamin K be administered. • In patients initiating VKA therapy, routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy is not recommended. • For VKA-associated major bleeding, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate is suggested over plasma. Additional use of vitamin K 5 to 10 mg administered by slow IV injection is

Clinical Guideline	Recommendations
	recommended rather than reversal with coagulation factors alone. <u>Prevention of VTE in nonsurgical patients</u> • Acutely ill hospitalized medical patients at increased risk of thrombosis: anticoagulant thromboprophylaxis with LMWH, low dose UFH (two or three times daily), or fondaparinux is recommended. Choice should be based on patient preference, compliance, and ease of administration, as well as on local factors affecting acquisition costs. • Acutely ill hospitalized patients at low risk of thrombosis: pharmacologic or mechanical prophylaxis is not recommended. • Acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding: anticoagulant thromboprophylaxis is not recommended. • Acutely ill hospitalized medical patients at increased risk for thrombosis who are bleeding or at high risk of major bleeding: optimal use of mechanical thromboprophylaxis is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, it is suggested that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis. • Acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis: extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay is suggested against. • Critically ill patients: routine ultrasound screening for deep vein thrombosis (DVT) is suggested against. • Critically ill patients: use of LMWH or low dose UFH thromboprophylaxis is suggested over no prophylaxis. • Critically ill patients who are bleeding or are at high risk for major bleeding: use of mechanical thromboprophylaxis until the bleeding risk decreases is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, pharmacologic thromboprophylaxis is suggested to be substituted for mechanical thromboprophylaxis. • Outpatients with cancer who have no additional risk factors for VTE: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is not recommended. • Outpatients with solid tumors who have additional risk factors for VTE with low risk of bleeding: prophylaxis with LMWH or low dose UFH is suggested over no prophylaxis. • Outpatients with cancer and indwelling central venous catheters: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is suggested against. • Chronically immobilized patients residing at home or at a nursing home: routine thromboprophylaxis is suggested against. • Long distance travelers at increased risk of VTE: frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible is suggested. • Long distance travelers at increased risk of VTE: use of properly fitted, below-knee graduated compression stockings during travel is suggested. For all other long distance travelers, use of graduated compression stockings is suggested against. • Long distance travelers: use of aspirin or anticoagulants to prevent VTE is suggested against. • Patients with asymptomatic thrombophilia: long term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE is not recommended. <u>Prevention of VTE in nonorthopedic surgical patients</u> • General and abdominal-pelvic surgery patients at very low risk for VTE: no specific pharmacologic or mechanical prophylaxis is recommended for use

Clinical Guideline	Recommendations
	other than early ambulation. • General and abdominal-pelvic surgery patients at low risk for VTE: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are not at high risk major bleeding complications: LMWH, low dose UFH, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at high risk for VTE who are not at high risk for major bleeding complications: LMWH or low dose UFH is recommended over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • High-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications: extended duration (four weeks) of LMWH prophylaxis is recommended over limited duration prophylaxis. • High-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • General and abdominal-pelvic surgery patients at high risk for VTE in whom both LMWH and UFH are contraindicated or unavailable and who are not at high risk for major bleeding complications: low dose aspirin, fondaparinux, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients: it is suggested that an inferior vena cava filter not be used for primary VTE prevention. • General and abdominal-pelvic surgery patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. • Cardiac surgery patients with an uncomplicated postoperative course: mechanical prophylaxis is suggested over either no prophylaxis or pharmacologic prophylaxis. • Cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications: adding pharmacologic prophylaxis with low dose UFH or LMWH to mechanical prophylaxis is suggested. • Thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding: low dose UFH or LWMH is suggested over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • Thoracic surgery patients who are at high risk for major bleeding: mechanical prophylaxis over no prophylaxis is suggested until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • Craniotomy patients: mechanical prophylaxis is suggested over no prophylaxis or pharmacologic prophylaxis. • Craniotomy patients at very high risk for VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Patients undergoing spinal surgery: mechanical prophylaxis is suggested over no prophylaxis, UFH, or LMWH. • Patients undergoing spinal surgery at high risk of VTE: it is suggested that

Clinical Guideline	Recommendations
	pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Major trauma patients: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Major trauma patients at high risk for VTE: it is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis when not contraindicated by lower extremity injury. • Major trauma patients in whom LMWH and low dose UFH are contraindicated: mechanical prophylaxis is suggested over no prophylaxis when not contraindicated by lower extremity injury. It is suggested that either LMWH or low dose UFH be added when the risk of bleeding diminishes or the contraindication to heparin resolves. • Major trauma patients: it is suggested that an interior vena cava filter not be used for primary VTE prevention. • Major trauma patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. <u>Prevention of VTE in orthopedic surgery patients</u> • Total hip arthroplasty or total knee arthroplasty: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, aspirin, or an intermittent pneumatic compression device. • Hip fracture surgery: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, low dose UFH, adjusted-dose VKA, aspirin, or intermittent pneumatic compression device. • Patients undergoing major orthopedic surgery (total hip arthroplasty, total knee arthroplasty, hip fracture surgery) and receiving LMWH as thromboprophylaxis: it is recommended to start either 12 hours or more preoperatively or postoperatively rather than within four hours or less preoperatively or postoperatively. • Total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, or aspirin. • Hip replacement surgery, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, low dose UFH, adjusted-dose VKA, or aspirin. • Major orthopedic surgery: it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days. • Major orthopedic surgery: it is suggested to use dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the hospital stay. • Major orthopedic surgery in patients at an increased risk of bleeding: intermittent pneumatic compression device or no prophylaxis is suggested over pharmacologic prophylaxis. • Major orthopedic surgery in patients who decline or are uncooperative with injections or intermittent pneumatic compression device: apixaban or dabigatran etexilate mesylate (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran etexilate mesylate are unavailable) is recommended over alternative forms of prophylaxis.

Clinical Guideline	Recommendations
	• Major orthopedic surgery in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical prophylaxis: inferior vena cava filter placement for primary prevention of VTE is suggested against over no thromboprophylaxis. • Asymptomatic patients following major orthopedic surgery: Doppler ultrasound screening before hospital discharge is not recommended. • Patients with lower leg injuries requiring leg immobilization: no prophylaxis is suggested rather than pharmacologic thromboprophylaxis. • Knee arthroscopy in patients without a history of prior VTE: no thromboprophylaxis is suggested rather than prophylaxis. <u>Antithrombotic therapy for VTE disease</u> • Acute DVT of the leg or pulmonary embolism (PE) treated with VKA therapy: initial treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) is recommended over no such initial treatment. • High clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment while awaiting the results of diagnostic tests. • Intermediate clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment if the results of diagnostic tests are expected to be delayed for more than four hours. • Low clinical suspicion of acute VTE or PE: it is suggested to not treat with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours. • Acute isolated distal DVT of the leg without severe symptoms or risk factors for extension: serial imaging of the deep veins for two weeks is suggested over initial anticoagulation. • Acute isolated distal DVT of the leg and severe symptoms or risk factors for extension: initial anticoagulation is suggested over serial imaging of the deep veins. • Acute isolated distal DVT of the leg in patients managed with initial anticoagulation: using the same approach as for patients with acute proximal DVT is recommended. • Acute isolated distal DVT of the leg who are managed with serial imaging: no anticoagulation if the thrombus does not extend is recommended; anticoagulation is suggested if the thrombus extends but remains confined to the distal veins; and anticoagulation is recommended if the thrombus extends into the proximal veins. • Acute DVT of the leg or PE: early initiation of VKA therapy is recommended over delayed initiation, and continuation of parenteral anticoagulation for a minimum on five days and until the INR is 2.0 or above for at least 24 hours. • Acute DVT of the leg or PE: LMWH or fondaparinux is suggested over IV or SC UFH. • Patients with acute DVT of the leg or PE receiving LMWH: once daily LMWH administration is suggested over twice daily administration. • Acute DVT of the leg and home circumstances are adequate: initial treatment at home is recommended over treatment in hospital. • Low risk PE and home circumstances are adequate: early discharge is suggested over standard discharge. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over catheter-directed thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over systemic thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over venous thrombectomy.

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	• Acute DVT of the leg in patients who undergo thrombosis removal: the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal is recommended. • Acute DVT of the leg: use of an inferior vena cava filter in addition to anticoagulants is not recommended. • Acute proximal DVT of the leg in patients with contraindication to anticoagulation: use of an inferior vena cava filter is recommended. • Acute proximal DVT of the leg in patients with an inferior vena cava filter inserted as an alternative to anticoagulation: a conventional course of anticoagulant therapy is suggested if the risk of bleeding resolves. • Acute DVT of the leg: early ambulation is suggested over initial bed rest. • Acute VTE in patients receiving anticoagulant therapy: long term therapy is recommended over stopping anticoagulant therapy after about one week of initial therapy. • Acute symptomatic DVT of the leg: compression stockings are suggested. • Acute PE associated with hypotension in patients who do not have a high bleeding risk: systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension: systemically administered thrombolytic therapy is not recommended. • In selected patients with acute PE not associated with hypotension and with a low bleeding risk who initial clinical presentation or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension: administration of thrombolytic therapy is suggested. • Proximal DVT of the leg or PE provoked by surgery: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment of a longer time limited period, or extended therapy. • Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment for a longer time limited period, extended therapy if there is high bleeding risk. Anticoagulation treatment for three months is suggested over extended therapy if there is a low or moderate bleeding risk. • Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor: treatment with anticoagulation for three months is suggested over treatment for a shorter period, and anticoagulation treatment for three months is recommended over treatment of longer time limited period or extended therapy. • Unprovoked DVT of the leg or PE: treatment with anticoagulation for three months is recommended over treatment of a shorter duration. After three months, patients should be evaluated for the risk-benefit ratio of extended therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a low or moderate bleeding risk: extended anticoagulant therapy is suggested over three months of therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a high bleeding risk: three months of anticoagulant therapy is recommended over extended therapy. • First VTE that is an unprovoked isolated distal DVT of the leg: three months of anticoagulation therapy is suggested over extended therapy in those with a low or moderate bleeding risk, and three months of anticoagulant treatment is recommended in those with a high bleeding risk. • Second unprovoked VTE or PE: extended anticoagulant therapy is recommended over three months of therapy in those who have a low bleeding risk, and extended anticoagulant therapy is suggested in patients with a

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	moderate bleeding risk. • Second unprovoked VTE or PE in patients with a high bleeding risk: three months of anticoagulant therapy is suggested over extended therapy. • DVT of the leg or PE and active cancer: if the risk of bleeding is not high, extended anticoagulation therapy is recommended over three months of therapy, and if there is a high bleeding risk, extended anticoagulant therapy is suggested. • DVT of the leg or PE in patients treated with VKA: a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended over a lower (<2.0) or higher (range, 3.0 to 5.0) range for all treatment durations. • DVT of the leg or PE in patients with no cancer: VKA therapy is suggested over LMWH for long-term therapy. For patients with DVT or PE and no cancer who are not treated with VKA therapy, LMWH is suggested over dabigatran etexilate mesylate or rivaroxaban for long term therapy. • DVT of the leg or PE and cancer: LMWH is suggested over VKA therapy. In patients with DVT of the leg or PE and cancer who are not treated with LMWH, VKA is suggested over dabigatran etexilate mesylate or rivaroxaban for long-term therapy. • DVT of the leg or PE in patients who receive extended therapy: treatment with the same anticoagulant chosen for the first three months is suggested. • Patients incidentally found to have asymptomatic DVT of the leg or PE: treatment with the same anticoagulant is suggested as for comparable patients with symptomatic DVT or PE. • In patients with chronic thromboembolic pulmonary hypertension, extended anticoagulation is recommended over stopping therapy. • Superficial vein thrombosis of the lower limb of at least 5 cm in length: use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation. • Superficial vein thrombosis in patients treated with anticoagulation: fondaparinux 2.5 mg/day is suggested over a prophylactic dose of LMWH. • Upper-extremity DVT that involves the axillary or more proximal veins: acute treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) over no such acute treatment. • Acute upper-extremity DVT that involves the axillary or more proximal veins: LMWH or fondaparinux is suggested over IV or SC UFH, and anticoagulation therapy alone is suggested over thrombolysis. • Upper-extremity DVT in patients undergoing thrombolysis: the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis is recommended. • In most patients with upper-extremity DVT that is associated with a central venous catheter: it is suggested that the catheter not be removed if it is functional and there is an ongoing need for the catheter. • Upper-extremity DVT that involves the axillary or more proximal veins: a minimum duration of anticoagulation of three months is suggested over a shorter duration. • Upper-extremity DVT that is associated with a central venous catheter that is removed: three months of anticoagulation is recommended over a longer duration of therapy in patients with no cancer, and this is suggested in patients with cancer. • Upper-extremity DVT that is associated with a central venous catheter that is not removed: it is recommended that anticoagulation is continued as long as the central venous catheter remains over stopping after three months of treatment in patients with cancer, and this is suggested in patients with no cancer. • Upper-extremity DVT that is not associated with a central venous catheter or

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	with cancer: three months of anticoagulation is recommended over a longer duration of therapy. • Acute symptomatic upper-extremity DVT: use of compression sleeves or venoactive medications is suggested against. • Symptomatic splanchnic vein thrombosis: anticoagulation is recommended over no anticoagulation. • Symptomatic hepatic vein thrombosis: anticoagulation is suggested over no anticoagulation. • In patients with incidentally detected splanchnic vein thrombosis or hepatic vein thrombosis: no anticoagulation is suggested over anticoagulation. <u>Antithrombotic therapy for atrial fibrillation (AF)</u> • Patients with AF, including those with paroxysmal AF, who are at low risk of stroke: no therapy is suggested over antithrombotic therapy. For patients who choose antithrombotic therapy, aspirin is suggested over oral anticoagulation or combination therapy with aspirin and clopidogrel. • Patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke: oral anticoagulation is recommended over no therapy. Oral anticoagulation is suggested over aspirin or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel are suggested over aspirin. • Patients with AF, including those with paroxysmal AF, who are at high risk of stroke: oral anticoagulation is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel is recommended over aspirin. • Patients with AF, including those with paroxysmal AF: for recommendations in favor of oral anticoagulation, dabigatran etexilate mesylate 150 mg twice daily is suggested over adjusted-dose VKA therapy (target INR range, 2.0 to 3.0). • Patients with AF and mitral stenosis: adjusted-dose VKA therapy is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take adjusted-dose VKA therapy, combination therapy with aspirin and clopidogrel is recommended over aspirin alone. • Patients with AF and stable coronary artery disease and who choose oral anticoagulation: adjusted-dose VKA therapy alone is suggested over the combination of adjusted-dose VKA therapy and aspirin. • Patients with AF at high risk of stroke during the first month after placement of a bare-metal stent or the first three to six months after placement of a drug-eluting stent: triple therapy (e.g., VKA therapy, aspirin, and clopidogrel) is suggested over dual antiplatelet therapy (e.g., aspirin and clopidogrel). After this initial period, a VKA plus a single antiplatelet agent is suggested over a VKA alone. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate risk of stroke during the first 12 months after placement of a stent: dual antiplatelet therapy is suggested over triple therapy. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate to high risk of stroke who experience an acute coronary syndrome (ACS) and do not undergo stent placement, for the first 12 months: adjusted-dose VKA therapy plus single antiplatelet therapy is suggested over dual antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable

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	coronary artery disease. • Patients with AF at low risk of stroke: dual antiplatelet therapy is suggested over adjusted-dose VKA therapy plus single antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF being managed with a rhythm control strategy: it is suggested that antithrombotic therapy decisions follow the general risk-based recommendations for patients with nonrheumatic AF, regardless of the apparent persistence of normal sinus rhythm. • Patients with atrial flutter: it is suggested that antithrombotic therapy decisions follow the same risk-based recommendations as for AF. <u>Antithrombotic therapy for ischemic stroke</u> • In patients with acute ischemic stroke or transient ischemic attack (TIA), early (within 48 hours) aspirin 160 to 325 mg is recommended over therapeutic parenteral anticoagulation. • In patients with a history of noncardioembolic ischemic stroke or TIA, aspirin (75 to 100 mg daily), clopidogrel (75 mg daily), aspirin-dipyridamole extended-release (ER) (25 mg-200 mg twice daily) or cilostazol (100 mg twice daily) is recommended over oral anticoagulants, the combination of clopidogrel plus aspirin or triflusal. o Clopidogrel or aspirin-dipyridamole ER is recommended over aspirin or cilostazol. • In patients with a history of ischemic stroke or TIA and AF, oral anticoagulation with dabigatran 150 mg twice daily is recommended over VKA therapy. o In patients who are unable to or choose not to take an oral anticoagulant, the combination of aspirin plus clopidogrel is recommended over aspirin alone. <u>Primary and secondary prevention of cardiovascular disease</u> • Patients ≥50 years of age without symptomatic cardiovascular disease: low dose aspirin (75 to 100 mg/day) is suggested over no aspirin therapy. • Patients with established coronary artery disease: long term single antiplatelet therapy with aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended over no antiplatelet therapy, and single antiplatelet therapy is suggested over dual antiplatelet therapy. • Patients in the first year after ACS who have not undergone percutaneous coronary intervention (PCI): dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day or clopidogrel 75 mg/day plus low dose aspirin 75 to 100 mg/day) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients in the first year after an ACS who have undergone PCI with stent placement: dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day, clopidogrel 75 mg/day plus low dose aspirin, or prasugrel 10 mg/day plus low dose aspirin) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients with anterior myocardial infarction (MI) and left ventricular thrombus, or at high risk for left ventricular thrombus, who do not undergo stenting: warfarin plus low dose aspirin (75 to 100 mg/day) is recommended over single antiplatelet therapy or dual antiplatelet therapy for the first three months. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, single antiplatelet therapy is recommended as per the established coronary

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	artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who undergo bare-metal stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for one month is suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the second and third month post-bare-metal stent is suggested over alternative regimens and alternative time frames for warfarin use. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus who undergo drug-eluting stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for up to three to six months is suggested over alternative regimens and alternative durations of warfarin therapy. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective PCI with placement of bare-metal stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for one month is recommended over single antiplatelet therapy. For the subsequent 11 months, dual antiplatelet therapy with combination low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. • Patients who have undergone elective PCI with placement of drug-eluting stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for three to six months is recommended over single antiplatelet therapy. After three to six months, continuation of dual antiplatelet therapy with low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested to be continued until 12 months over antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective bare-metal stent or drug-eluting stent placement: low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is recommended over cilostazol in addition to these drugs. Aspirin 75 to 100 mg/day or clopidogrel 75 mg/day as part of dual antiplatelet therapy is suggested over the use of either drug with cilostazol. Cilostazol 100 mg twice daily as a substitute for either low dose aspirin or clopidogrel as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class is suggested. • Patients with coronary artery disease undergoing elective PCI but no stent placement: for the first month dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients with systolic left ventricular dysfunction without established coronary artery disease and no left ventricular thrombus: it is suggested that antiplatelet therapy and warfarin not be used. • Patients with systolic left ventricular dysfunction without established coronary artery disease with identified acute left thrombus: moderate intensity warfarin for at least three months is suggested. • Patients with systolic left ventricular dysfunction and established coronary artery disease: recommendations are as per the established coronary artery

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	disease recommendations.
	
	<u>Antithrombotic therapy in peripheral artery disease (PAD)</u>
	• In patients with asymptomatic PAD, aspirin 75 to 100 mg daily is recommended.
	• In patients with symptomatic PAD, long-term therapy with aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) is recommended for secondary prevention of cardiovascular events. Dual antiplatelet therapy or the combination of an antiplatelet agent with moderate-intensity warfarin is not recommended.
	• Use of cilostazol in addition to aspirin or clopidogrel is recommended in patients with intermittent claudication refractory to exercise therapy and smoking cessation.
	• Use of prostanoids in addition to aspirin or clopidogrel is recommended in patients with symptomatic PAD and critical leg ischemia who are not candidates for vascular intervention.
	• In patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, long-term therapy with aspirin or clopidogrel is recommended over dual antiplatelet therapy.
	• Following peripheral artery bypass graft surgery, long-term therapy with aspirin or clopidogrel is recommended over the combination of antiplatelet agent plus warfarin. Clopidogrel plus aspirin for one year is recommended in patients undergoing below-knee bypass graft surgery with prosthetic grafts.
	• In patients with asymptomatic carotid stenosis, aspirin 75 to 100 mg daily is recommended.
	• In patients with symptomatic carotid stenosis, long-term therapy with clopidogrel (75 mg daily) or aspirin/dipyridamole ER (25 mg/200 mg twice daily) is recommended over aspirin (75 to 100 mg daily).
	
	<u>Antithrombotic and thrombolytic therapy for valvular disease</u>
	• Antithrombotic therapy in the first three months after surgery:
	  ○ In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, aspirin (50 to 100 mg/day) over VKA therapy is suggested in the first three months.
	  ○ In patients with transcatheter aortic bioprosthetic valves, aspirin (50 to 100 mg/day) plus clopidogrel (75 mg/day) is suggested over VKA therapy and over no antiplatelet therapy in the first three months.
	  ○ In patients with a bioprosthetic valve in the mitral position, VKA therapy over no VKA therapy for the first three months after valve insertion is suggested.
	• Long-term antithrombotic therapy for patients with bioprosthetic valves:
	  ○ In patients with bioprosthetic valves in normal sinus rhythm, aspirin therapy over no aspirin therapy after three months postoperative is suggested.
	• Early postoperative bridging to intermediate/long-term therapy (postoperative day 0 to 5):
	  ○ In patients with mechanical heart valves, bridging with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) over intravenous (IV) therapeutic UFH until stable on VKA therapy.
	• Long-term antithrombotic therapy for patients with mechanical valves:
	  ○ VKA therapy is recommended over no VKA therapy for long-term management.
	• Intensity of VKA therapy for patients with mechanical aortic valve prostheses:
	  ○ VKA therapy at a target of 2.5 over lower targets is suggested. A target of 2.5 is recommended over higher targets.

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	• Intensity of VKA therapy for patients with mechanical mitral valve prostheses:
	  o VKA therapy with a target of 3.0 over lower INR targets is suggested.
	• Intensity of VKA therapy in patients with double mechanical valve or with additional risk factors:
	  o VKA therapy with a target of 3.0 is suggested over target INR 2.5.
	• Antiplatelet agent in addition to VKA therapy for patients with mechanical aortic or mitral valve prostheses:
	  o Patients who are at low risk of bleeding, adding over not adding an antiplatelet agent such as low-dose (50 to 100 mg/day) to VKA therapy is suggested.
	• For patients with mechanical aortic or mitral valves VKA therapy over antiplatelet agents is recommended.
	• In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, the use of antiplatelet therapy for the first three months is suggested over VKA therapy.
	• In patients undergoing aortic valve repair, aspirin (50 to 100 mg/day) is suggested over VKA therapy.

American College of Chest Physicians: **Antithrombotic Therapy for VTE Disease (2016, 2021 Update)**[9-10]	<u>Choice of long-term (first three months) and extended (no scheduled stop date) anticoagulant</u> • In patients with proximal deep vein thrombosis (DVT) or pulmonary embolism (PE), long-term (three months) anticoagulant therapy is recommended over no such therapy. • In patients with DVT of the leg or PE and no cancer, as long-term (first three months) anticoagulant therapy, dabigatran, rivaroxaban, apixaban, or edoxaban is recommended over vitamin K antagonist (VKA) therapy. • No non-vitamin K oral anticoagulant is preferred over another. • Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. • In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term anticoagulant therapy, LMWH is recommended over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban. • In patients with DVT of the leg or PE who receive extended therapy, there is no need to change the choice of anticoagulant after the first three months. <u>Duration of anticoagulant therapy</u> • In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension, suggest serial imaging of the deep veins for two weeks over anticoagulation or (ii) with severe symptoms or risk factors for extension. suggest anticoagulation over serial imaging of the deep veins. • In patients with acute isolated distal DVT of the leg who are managed with serial imaging, (i) recommend no anticoagulation if the thrombus does not extend, (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins, and (iii) recommend anticoagulation if the thrombus extends into the proximal veins. • In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE, suggest clinical surveillance over anticoagulation or (ii) high risk for recurrent VTE, suggest anticoagulation over clinical surveillance. • In patients who are incidentally found to have asymptomatic PE, suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE. • In patients with cerebral vein/venous sinus thrombosis, recommend anticoagulation therapy for at least the treatment phase (first three months)

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	over no anticoagulant therapy. • In patients with acute DVT of the leg, suggest anticoagulant therapy alone over interventional (thrombolytic, mechanical, or pharmaco-mechanical) therapy. • In patients with acute PE associated with hypotension (e.g., systolic BP <90 mmHg) who do not have a high bleeding risk, suggest systemically administered thrombolytic therapy over no such therapy. • In most patients with acute PE not associated with hypotension, recommend against systemically administered thrombolytic therapy. • In patients with a proximal DVT of the leg or PE provoked by surgery, treatment with anticoagulation for three months is recommended over (i) treatment of a shorter period, (ii) treatment of a longer time-limited period (e.g., six, 12, or 24 months), or (iii) extended therapy (no scheduled stop date). • In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, treatment with anticoagulation for three months is recommended over (i) treatment of a shorter period and (ii) treatment of a longer time-limited period (e.g., six, 12, or 24 months). Treatment with anticoagulation for three months is suggested over extended therapy if there is a low or moderate bleeding risk, and treatment for three months is recommended over extended therapy if there is a high risk of bleeding. • In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, treatment with anticoagulation for three months is suggested over treatment of a shorter period, treatment with anticoagulation for three months is recommended over treatment of a longer time-limited period (e.g., six, 12, or 24 months), and treatment with anticoagulation for three months is recommended over extended therapy (no scheduled stop date). • In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, treatment with anticoagulation for at least three months is recommended over treatment of a shorter duration), and treatment with anticoagulation for three months is recommended over treatment of a longer time-limited period (e.g., six, 12, or 24 months). • In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk, extended anticoagulant therapy (no scheduled stop date) is suggested over three months of therapy, and (ii) high bleeding risk, three months of anticoagulant therapy is recommended over extended therapy (no scheduled stop date). • In patients with a second unprovoked VTE and who have a (i) low bleeding risk, extended anticoagulant therapy (no scheduled stop date) is recommended over three months; (ii) moderate bleeding risk, extended anticoagulant therapy is suggested over three months of therapy; or (iii) high bleeding risk, three months of anticoagulant therapy is suggested over extended therapy (no scheduled stop date). • In patients with "cancer-associated thrombosis" and who (i) do not have a high bleeding risk, extended anticoagulant therapy (no scheduled stop date) is recommended over three months of therapy, or (ii) have a high bleeding risk, extended anticoagulant therapy (no scheduled stop date) is suggested over three months of therapy. • In patients with acute VTE who do not have a contraindication, a three-month treatment phase of anticoagulation is recommended. <u>Extended-phase therapy</u> • In patients with VTE diagnosed in the setting of a major or minor transient risk factor, offering extended-phase anticoagulation is not recommended. • In patients with VTE diagnosed in the absence of transient provocation (unprovoked VTE or provoked by persistent risk factor), offering extended-

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	phase anticoagulation with a direct-acting oral anticoagulant (DOAC) is recommended. • In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, offering extended-phase anticoagulation with a VKA is suggested. • Extended-phase anticoagulation does not have a predefined stop date. However, studies of extended-phase anticoagulation followed patients for durations of about two to four years. Although most patients in these studies did not stop anticoagulation therapy at the end of follow-up, the risk-to-benefit balance of continuing extended anticoagulation therapy beyond this time is uncertain. • In patients offered extended-phase anticoagulation, the use of reduced-dose apixaban or rivaroxaban is suggested over full-dose apixaban or rivaroxaban. • In patients offered extended-phase anticoagulation, reduced-dose DOAC is recommended over aspirin or no therapy and rivaroxaban is suggested over aspirin. • In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin is suggested over no aspirin to prevent recurrent VTE. <u>Aspirin for extended treatment of VTE</u> • In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin is suggested over no aspirin to prevent recurrent VTE. <u>Whether to anticoagulate subsegmental PE</u> • In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE, clinical surveillance is suggested over anticoagulation or (ii) high risk for recurrent VTE, anticoagulation is suggested over clinical surveillance. <u>Treatment of acute PE out of the hospital</u> • In patients with low-risk PE and whose home circumstances are adequate, treatment at home or early discharge is suggested over standard discharge (e.g., after the first five days of treatment). <u>Systemic thrombolytic therapy for PE</u> • In patients with acute PE associated with hypotension (e.g., systolic BP <90 mm Hg) who do not have a high bleeding risk, systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension, systemically administered thrombolytic therapy is NOT recommended. • In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, systemically administered thrombolytic therapy is suggested over no such therapy. <u>Thrombolytic therapy in patients with upper extremity DVT</u> • In patients with acute upper extremity DVT (UEDVT) that involves the axillary or more proximal veins, anticoagulant therapy alone is suggested over thrombolysis. • In patients with UEDVT who undergo thrombolysis, the same intensity and duration of anticoagulant therapy as in patients with UEDVT who do not undergo thrombolysis is recommended.

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	Management of recurrent VTE on anticoagulant therapy • In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), switching to treatment with LMWH at least temporarily is suggested. • In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), increasing the dose of LMWH by about one-quarter to one-third is suggested. • Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy. A temporary switch to LMWH will usually be for at least one month.
American Heart Association/American Stroke Association: **Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation: A Science Advisory for Healthcare Professionals (2012)**[11]	Prevention of stroke in nonvalvular AF • Apixaban, dabigatran etexilate mesylate, rivaroxaban and warfarin are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF. • The choice of antithrombotic treatment should be individualized based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range if the patient has been taking warfarin. • Dabigatran etexilate mesylate 150 mg twice daily is an efficacious alternative to warfarin for the prevention of first and recurrent stroke in patients with nonvalvular AF who have at least one additional risk factor and a creatinine clearance (CrCl) >30 mL/min. • The use of dabigatran etexilate mesylate 75 mg twice daily in patients with AF and at least one additional risk factor who have a low CrCl (15 to 30 mL/min) may be considered, but its safety and efficacy have not been established. The use of dabigatran etexilate mesylate in patients with more severe renal failure is not recommended in patients with a CrCl <15 mL/min. • Apixaban 5 mg twice daily is an effective alternative to aspirin in patients with nonvalvular AF deemed unsuitable for VKA therapy with one or more additional risk factor and no more than one of the following characteristics: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. • Although safety and efficacy have not been established, apixaban 2.5 mg twice daily may be considered as an alternative to aspirin in patients with nonvalvular AF deemed unsuitable for VKA therapy who have one or more additional risk factor and two or more of the following criteria: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. • Apixaban 5 mg twice daily is a relatively safe and efficacious alternative to warfarin in patients with nonvalvular AF deemed appropriate for VKA therapy that have one or more risk factors and no more than one of the following: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. • Apixaban should not be used if the CrCl is <25 mL/min. • In patients with nonvalvular AF who are at moderate to high risk of stroke (prior history of transient ischemic attack [TIA], stroke, or systemic embolization or have two additional risk factors), rivaroxaban 20 mg daily is a reasonable alternative to warfarin. • In patients with renal impairment and nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or two or more additional risk factors), with a CrCl 15 to 50 mL/min, rivaroxaban 15 mg daily may be considered; however, its safety and efficacy have not been established. • Rivaroxaban should not be used if the CrCl is <15 mL/min.

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	• The safety and efficacy of combining dabigatran, rivaroxaban, or apixaban with an antiplatelet agent have not been established.
American Heart Association/American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation (2014)**[12]	Recommendations for risk-based antithrombotic therapy: Class I • In patients with atrial fibrillation (AF), antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences (Level of Evidence: C). • Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent (Level of Evidence: B). • In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence: B). • For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) should be based on type and location of the prosthesis (Level of Evidence: B). • For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran, rivaroxaban, or apixaban (Level of Evidence: B). • For patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (Level of Evidence: A) • For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor is recommended (Level of Evidence: C). • Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks (Level of Evidence: C). • Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding (Level of Evidence: C). • For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated (Level of Evidence: C). • Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (Level of Evidence: B). • For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF (Level of Evidence: C). Class IIa • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Level of Evidence: B). • For patients with nonvalvular AF with a CHA_2DS_2-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (Level of Evidence: B). Class IIb • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence: C). • For patients with nonvalvular AF and moderate-to-severe chronic kidney

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	disease with a CHA_2DS_2-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established (Level of Evidence: C). • In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture (Level of Evidence: C). • Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B). Class III: No Benefit • The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (Level of Evidence: C). Class III: Harm • The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (Level of Evidence: B). <u>Recommendations for rate control:</u> Class I • Control of the ventricular rate using a beta blocker or nondihydropyridine (non-DHP) calcium channel blocker (CCB) is recommended for patients with paroxysmal, persistent, or permanent AF (Level of Evidence: B). • Intravenous administration of a beta blocker or non-DHP CCB is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Level of Evidence: B). • In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range (Level of Evidence: C). Class IIa • A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF (Level of Evidence: B). • Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (Level of Evidence: B). • Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (Level of Evidence: B). Class IIb • A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and left ventricular systolic function is preserved (Level of Evidence: B). • Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated (Level of Evidence: C). Class III: Harm • AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications (Level of Evidence: C). • Non-DHP CCBs should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise (Level of Evidence: C).

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	• In patients with pre-excitation and AF, digoxin, non-DHP CCBs, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation. (Level of Evidence: B). • Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death (Level of Evidence: B). <u>Recommendations for Thromboembolism Prevention</u>: Class I • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method used to restore sinus rhythm (Level of Evidence: B). • For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated (Level of Evidence: C). • For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy (Level of Evidence: C). • Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile (Level of Evidence: C). Class IIa • For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks (Level of Evidence: B). • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion (Level of Evidence: C). Class IIb • For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation (Level of Evidence: C). <u>Recommendations for pharmacological cardioversion</u> Class I • Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Level of Evidence: A). Class IIa • Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF (Level of Evidence: A). • Propafenone or flecainide (“pill-in-the-pocket”) in addition to a beta blocker or

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	non-DHP CCB is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (Level of Evidence: B). Class III: Harm • Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes (Level of Evidence: B). <u>Recommendations for antiarrhythmic drugs to maintain sinus rhythm</u> Class I • Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended (Level of Evidence: C). • The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Level of Evidence: A): o Amiodarone o Dofetilide o Dronedarone o Flecainide o Propafenone o Sotalol • The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug (Level of Evidence: C). • Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated (Level of Evidence: C). Class IIa • A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy (Level of Evidence: C). Class IIb • It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF (Level of Evidence: C). Class III: Harm • Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent (Level of Evidence: C), including dronedarone (Level of Evidence: B). • Dronedarone should not be used for treatment of AF in patients with New York Heart Association class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks. (Level of Evidence: B). <u>Upstream therapy</u> Class IIa • An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF with reduced left ventricular ejection fraction (Level of Evidence: B). Class IIb • Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (Level of Evidence: B). • Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (Level of Evidence: A). Class III: No Benefit

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	• Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (Level of Evidence: B). (Class denotes strength of recommendation)

American Heart Association/American College of Cardiology/ Heart Rhythm Society: **2019 Focused Update of the 2014 Guideline for the Management of Patients with Atrial Fibrillation (2019)**[13]	<u>Recommendations for selecting an anticoagulant regimen</u>
	• For patients with atrial fibrillation (AF) and an elevated CHA_2DS_2-VASc score of two or greater in men or three or greater in women, oral anticoagulants are recommended. Options include:
	  ○ Warfarin
	  ○ Dabigatran
	  ○ Rivaroxaban
	  ○ Apixaban
	  ○ Edoxaban
	• Non–vitamin K oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).
	• Among patients treated with warfarin, the international normalized ratio (INR) should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable.
	• In patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), the CHA_2DS_2-VASc score is recommended for assessment of stroke risk.
	• For patients with AF who have mechanical heart valves, warfarin is recommended.
	• Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.
	• Renal function and hepatic function should be evaluated before initiation of a NOAC and should be reevaluated at least annually.
	• In patients with AF, anticoagulant therapy should be individualized on the basis of shared decision-making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient's values and preferences.
	• For patients with atrial flutter, anticoagulant therapy is recommended according to the same risk profile used for AF.
	• Reevaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risks.
	• For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended.
	• For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy.
	• For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.
	• For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD (serum creatinine ≥1.5 mg/dL [apixaban], CrCl 15 to 30 mL/min [dabigatran], CrCl <50 mL/min [rivaroxaban], or CrCl 15 to 50 mL/min [edoxaban]) with an elevated CHA_2DS_2-VASc score, treatment with reduced doses of direct thrombin or

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	factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, apixaban, or edoxaban). • For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered. • In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk. • The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve. <u>Interruption and bridging anticoagulation</u> • Bridging therapy with unfractionated heparin or low-molecular-weight heparin is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding. • For patients with AF without mechanical heart valves who require interruption of warfarin for procedures, decisions about bridging therapy (unfractionated heparin or low-molecular-weight heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated. • Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure. • Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding. <u>Rhythm control: recommendations for prevention of thromboembolism</u> • For patients with AF or atrial flutter of 48 hours' duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0), a factor Xa inhibitor, or direct thrombin inhibitor is recommended for at least three weeks before and at least four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score or the method (electrical or pharmacological) used to restore sinus rhythm. • For patients with AF or atrial flutter of more than 48 hours' duration or unknown duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated. • After cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile and bleeding risk profile. • For patients with AF or atrial flutter of less than 48 hours' duration with a CHA_2DS_2-VASc score of 2 or greater in men and 3 or greater in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor is reasonable as soon as possible before cardioversion, followed by long-term anticoagulation therapy. • For patients with AF or atrial flutter of 48 hours' duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform transesophageal echocardiography before cardioversion and proceed with cardioversion if no left atrial thrombus is identified, including in the LAA, provided that anticoagulation is achieved before transesophageal echocardiography and maintained after cardioversion for at least four weeks. • For patients with AF or atrial flutter of less than 48 hours' duration with a CHA_2DS_2-VASc score of 0 in men or 1 in women, administration of heparin, a

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	factor Xa inhibitor, or a direct thrombin inhibitor, versus no anticoagulant therapy, may be considered before cardioversion, without the need for postcardioversion oral anticoagulation. <u>Recommendations for AF complicating acute coronary syndrome (ACS)</u> • For patients with ACS and AF at increased risk of systemic thromboembolism (based on CHA_2DS_2-VASc risk score of 2 or greater), anticoagulation is recommended unless the bleeding risk exceeds the expected benefit. • Urgent direct-current cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control. • Intravenous beta blockers are recommended to slow a rapid ventricular response to AF in patients with ACS who do not display HF, hemodynamic instability, or bronchospasm. • If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone percutaneous coronary intervention (PCI) with stenting for ACS, it is reasonable to choose clopidogrel in preference to prasugrel. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist is reasonable to reduce the risk of bleeding as compared with triple therapy. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with $P2Y_{12}$ inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily is reasonable to reduce the risk of bleeding as compared with triple therapy. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with triple therapy. • If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF who are at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) and who have undergone PCI with stenting (drug eluting or bare metal) for ACS, a transition to double therapy (oral anticoagulant and $P2Y_{12}$ inhibitor) at four to six weeks may be considered. • Administration of amiodarone or digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability. • Administration of nondihydropyridine calcium antagonists may be considered to slow a rapid ventricular response in patients with ACS and AF only in the absence of significant HF or hemodynamic instability.
European Heart Rhythm Association and European Society of Cardiology Working Group on Thrombosis, endorsed by the Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa, Heart Rhythm Society, Asia Pacific Heart Rhythm	<u>Mitral valve repair</u> • Well managed vitamin K antagonist (VKA) monotherapy with good anticoagulation control (e.g. time in therapeutic range >65 to 70%), is generally recommended, taking into account the type of valve, the position, and additional risk factor(s), including atrial fibrillation. • Patients with a bioprosthetic valve and atrial fibrillation require lifelong oral anticoagulation (OAC). <u>Indications of 'add on' antiplatelet therapy in patients with atrial fibrillation and prosthetic mechanical heart valves</u> • In patients with a mechanical prosthetic valve and concomitant atrial

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Society, South African Heart Association, and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología: **Antithrombotic Therapy in Atrial Fibrillation Associated with Valvular Heart Disease (2017)**[14]	fibrillation (AF) with vascular disease, VKA plus low-dose aspirin (75 to 100 mg daily) may be considered in the absence of high bleeding risk. • In patients with a mechanical prosthetic valve and AF, when VKA plus aspirin are used, the INR should be kept between 2.0 and 3.0 (target 2.5), given the high bleeding risk of the combination and the lack of evidence of greater protection with higher intensity VKA (INR range 3 to 5 or above). • High doses of aspirin (≥325 mg) in association with VKA at any intensity must be avoided. <u>Evidence for non-vitamin K antagonist oral anticoagulants (NOACs) use in patients with atrial fibrillation and valvular heart disease</u> • The use of the NOACs in patients with AF and mechanical valve prosthesis is contraindicated. • Randomized clinical trials testing the efficacy and safety of direct oral factor Xa inhibitors in patients with AF and mechanical heart valved prosthesis are lacking. Until more data are available, rivaroxaban, apixaban, and edoxaban are contraindicated in such patients. • Until more data are available, AF patients with any degree of rheumatic mitral valve stenosis and those with moderate-to-severe non-rheumatic mitral stenosis should not be treated with NOACs. • The efficacy and safety of NOACs for stroke/systemic embolism (SE) prevention may be similar in AF patients with and without conservative valve surgery such as annuloplasty, commissurotomy or valvuloplasty, or bioprosthetic valves based on small numbers of patients in post hoc analyses of RCTs. More data are needed to define the role of NOACs in this setting. • The efficacy and safety of NOACs in patients with non-rheumatic mitral and/or aortic regurgitation or other native VHD may be similar to AF patients without VHD based on small numbers of patients in post hoc analyses of RCTs. More data are needed to define the role of NOACs in this setting. • In patients with hemodynamically insignificant valve disease and in those who have had prior successful balloon mitral valvulotomy, NOACs can be considered as substitute for VKAs. <u>Antithrombotic therapy in patients with atrial fibrillation undergoing trans-aortic valve intervention or left atrial appendage occlusion</u> • AF patients who underwent successful trans-aortic valve intervention (TAVI) may be treated with Xa inhibitors; however data are limited. • AF patients with stable coronary artery disease who underwent TAVI may be treated with OAC only, including VKA and Xa inhibitors; however prospective data are limited. • Based on trial protocols, OAC and single antiplatelet therapy after successful left atrial appendage occlusion (LAAO) may be used up to six weeks in low bleeding risk patients, followed by single antiplatelet therapy; however, long term data are limited, nor any comparison with NOACs. • Single antiplatelet therapy or no antithrombotic therapy may be used after LAAO in AF patients who are not eligible for VKA; however, long term data are limited, nor any comparison with NOACs. <u>Antithrombotic therapy for valvular atrial fibrillation in pregnant women</u> • There is no consensus on the optimal regimen for anticoagulation in peripartum women with mechanical valve prosthesis with AF. • As the optimal anticoagulation regimen for use in pregnancy and peripartum remains undetermined, all decisions should be made by a fully informed mother and partner in consultation with a multidisciplinary team.
American Association	<u>Recommended prevention strategies for all postoperative atrial fibrillation (POAF)</u>

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for Thoracic Surgery: **2014 AATS Guidelines for the Prevention and Management of Peri-Operative Atrial Fibrillation and Flutter (POAF) for Thoracic Surgical Procedures (2014)[15]**	<u>patients</u> • Patients taking β-blockers prior to thoracic surgery should continue them in the postoperative period to avoid β-blockade withdrawal. • Intravenous magnesium supplementation may be considered to prevent postoperative AF when serum magnesium level is low or it is suspected that total body magnesium is depleted. • Digoxin should not be used for prophylaxis against AF. <u>Recommended prevention strategies for intermediate to high-risk POAF patients</u> • It is reasonable to administer diltiazem to those patients with preserved cardiac function who are not taking β-blockers preoperatively in order to prevent POAF. • It is reasonable to consider the postoperative administration of amiodarone to reduce the incidence of POAF for intermediate and high risk patients undergoing pulmonary resection. • Postoperative administration of intravenous amiodarone may be considered to prevent POAF in patients undergoing esophagectomy. • Atorvastatin may be considered to prevent POAF for statin naïve patients scheduled for intermediate and high risk thoracic surgical procedures. <u>Rate control recommendations for patients with new onset POAF</u> • Intravenous administration of beta-blockers (e.g., esmolol or metoprolol) or nondihydropyridine calcium channel blockers (diltiazem or verapamil) is recommended to achieve rate control (heart rate ≤110 bpm) for patients who develop POAF with rapid ventricular response. • Caution should be used with patients with hypotension, left ventricular (LV) dysfunction, or heart failure. • Combination use of atrioventricular (AV) nodal blocking agents, such as beta-blockers (e.g., esmolol or metoprolol), nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, can be useful to control heart rates when a single agent fails to control rates of POAF. The choice should be individualized and doses modified to avoid bradycardia. • For patients with hypotension, heart failure or LV dysfunction, or when other measures are unsuccessful or contraindicated, intravenous amiodarone can be useful for control of heart rate. Amiodarone could result in conversion to sinus rhythm, and if it is initiated after 48 hours of AF, both a transesophageal echocardiography (TEE) when possible, to rule out left atrial/LA appendage (LA/LAA) thrombus, and full anticoagulation should be considered. • For patients with heart failure, LV dysfunction or hypotension, intravenous digoxin may be considered for rate control of POAF. • For patients with ventricular preexcitation (i.e., Wolff-Parkinson-White syndrome) and POAF, use of AV nodal blocking agents, such as beta-blockers (e.g., esmolol or metoprolol), intravenous amiodarone, nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, should be avoided. <u>Recommendations for the use of antiarrhythmic drugs for pharmacologic cardioversion of POAF</u> • Restoration of sinus rhythm with pharmacologic cardioversion is reasonable in patients with symptomatic, hemodynamically stable POAF. Intravenous amiodarone can be useful for pharmacologic cardioversion of POAF. • It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm for patients with recurrent or refractory POAF. • Amiodarone, sotalol, flecainide, propafenone, or dofetilide can be useful to maintain sinus rhythm in patients with POAF, depending on underlying heart

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	disease, renal status and other comorbidities. • Flecainide or propafenone may be considered for pharmacologic cardioversion of POAF and maintenance of sinus rhythm if the patient has had no prior history of myocardial infarction, coronary artery disease, impaired LV function, significant LV hypertrophy, or valvular heart disease that is considered moderate or greater. These agents may need to be combined with an AV nodal blocking agent. • Intravenous ibutilide or procainamide may be considered for pharmacologic conversion of POAF for patients with structural heart disease and new onset POAF, but no hypotension or manifestations of congestive heart failure. Serum electrolytes and QTc interval must be within a normal range and patients must be closely monitored during and for at least six hours after the infusion if either ibutilide or procainamide. • Intravenous ibutilide or procainamide may be considered for patients with POAF and an accessory pathway. • Flecainide and propafenone should not be used to treat POAF in patients with a history of a prior myocardial infarction, coronary artery disease, and/or severe structural heart disease, including severe left ventricular hypertrophy, or significantly reduced left ventricular ejection fraction. • Dronedarone should not be used for treatment of POAF in patients with heart failure. <u>Recommendations for prevention of thromboembolism for patients with stable atrial fibrillation/flutter undergoing direct current cardioversion</u> • For stable patients with POAF of 48-hours duration or longer, anticoagulation (with warfarin for INR 2.0 to 3.0, a novel oral anti-coagulant [NOAC] or LMWH) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the method (electrical or pharmacological) used to restore sinus rhythm. • During the first 48 hours after the onset of POAF, the need for anticoagulation before and after direct current (DC) cardioversion may be based on the patient's risk of thromboembolism (CHA_2DS_2-VASc score) balanced by the risk of postoperative bleeding. • For POAF lasting longer than 48 hours, as an alternative to three weeks of therapeutic anticoagulation prior to cardioversion of POAF, it is reasonable to perform TEE in search of thrombus in the LA or LA appendage, preferably with full anticoagulation at the time of TEE in anticipation of DC cardioversion after the TEE. • For POAF lasting longer than 48 hours in patients who are not candidates for TEE (e.g., post-esophageal surgery), an initial rate control strategy combined with therapeutic anticoagulation using warfarin (aiming for INR 2.0 to 3.0), a direct thrombin inhibitor (e.g. dabigatran), factor Xa inhibitor (e.g. rivaroxaban, apixaban), or LMWH is recommended for at least three weeks prior to and four weeks after cardioversion. • Anticoagulation recommendations for cardioversion of atrial flutter are similar to those for atrial fibrillation. • For patients with an identified thrombus, cardioversion should not be performed until a longer period of anticoagulation is achieved (usually at least three weeks) and in accordance with established AF guidelines. <u>Management of anticoagulation for new onset POAF</u> • For the prevention of strokes for patients who develop POAF lasting longer than 48 hours, it is recommended to administer antithrombotic medications similarly to non-surgical patients. Anticoagulation within the first 48-hours of POAF should be considered based on the CHA_2DS_2-VASc risk score of the

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	patient for stroke weighed against the risk of postoperative bleeding. • New oral anticoagulants (dabigatran, rivaroxaban, apixaban) are reasonable as an alternative to warfarin for patients who do not have a prosthetic heart valve, hemodynamically significant valve disease, and/or severe renal impairment or risk of GI bleeding. • It is reasonable to continue anticoagulation therapy for four weeks after the return of sinus rhythm because of the possibility of slowly resolving impairment of atrial contraction with an associated ongoing risk for thrombus formation and for delayed embolic events. • New oral anticoagulants should be avoided for patients at risk for serious bleeding (including GI bleeding) as they cannot be readily reversed. However, their use may be recommended in situations where achievement of a therapeutic INR with warfarin has proved to be difficult.
The American Heart Association: **Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association (2011)[16]**	<u>Recommendations for initial anticoagulation for acute PE</u> • Therapeutic anticoagulation with SC LMWH, IV or SC UFH with monitoring, unmonitored weight-based SC UFH, or SC fondaparinux should be given to patients with objectively confirmed PE and no contraindications to anticoagulation. • Therapeutic anticoagulation during the diagnostic workup should be given to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation. Fibrinolysis is not recommended for undifferentiated cardiac arrest. <u>Recommendations for initial anticoagulation for patients with iliofemoral DVT</u> • In the absence of suspected or proven heparin induced thrombocytopenia, patients with iliofemoral DVT should receive therapeutic anticoagulation with IV UFH, SC UFH, a LMWH agent, or fondaparinux. • Patients with iliofemoral DVT who have suspected or proven heparin-induced thrombocytopenia should receive a direct thrombin inhibitor. <u>Recommendations for long-term anticoagulation therapy for patients with iliofemoral DVT</u> • Adult patients with iliofemoral DVT who receive oral warfarin as first-line long-term anticoagulation therapy should have warfarin overlapped with initial anticoagulation therapy for a minimum of five days and until the INR is >2.0 for at least 24 hours, and then targeted to an INR 2.0 to 3.0. • Patients with first episode iliofemoral DVT related to a major reversible risk factor should have anticoagulation stopped after three months. • Patients with recurrent or unprovoked iliofemoral DVT should have at least six months of anticoagulation and be considered for indefinite anticoagulation with periodic reassessment of the risks and benefits of continued anticoagulation. • Cancer patients with iliofemoral DVT should receive LMWH monotherapy for at least three to six months, or as long as the cancer or its treatment (e.g., chemotherapy) is ongoing. • In children with DVT, the use of LMWH monotherapy may be reasonable.
American College of Cardiology Foundation/ American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)[17]**	<u>Antiplatelet therapy to support primary PCI for STEMI</u> • Aspirin 162 to 325 mg should be given before primary PCI. • After PCI, aspirin should be continued indefinitely. • A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg. • $P2Y_{12}$ inhibitor therapy should be given for one year to patients with STEMI who receive a stent (bare-metal or drug-eluting) during primary PCI using clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily.

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	• It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI. • It is reasonable to start treatment with an IV GP IIb/IIIa receptor antagonist such as abciximab, high bolus-dose tirofiban or double-bolus eptifibatide at the time of primary PCI (with or without stenting or clopidogrel pre-treatment) in selected patients with STEMI who are receiving UFH. • It may be reasonable to administer IV GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended. • It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI. • Continuation of a $P2Y_{12}$ inhibitor beyond one year may be considered in patients undergoing drug-eluting stent placement. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. <u>Anticoagulant therapy to support primary PCI</u> • For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended: UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered or bivalirudin with or without prior treatment with UFH. • In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist. • Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis. <u>Adjunctive antiplatelet therapy with fibrinolysis</u> • Aspirin (162- to 325-mg loading dose) and clopidogrel (300 mg loading dose for ≤75 year of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy. • Aspirin should be continued indefinitely and clopidogrel (75 mg daily) should be continued for at least 14 days and up to one year in patients with STEMI who receive fibrinolytic therapy. • It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses after fibrinolytic therapy. <u>Adjunctive anticoagulant therapy with fibrinolysis</u> • Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the hospitalization, up to eight days or until revascularization if performed. • Recommended regimens include UFH administered as a weight-adjusted IV bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularization; enoxaparin administered according to age, weight, and creatinine clearance, given as an IV bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to eight days or until revascularization; or fondaparinux administered with initial IV dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 mL/min, for the duration of the index hospitalization, up to eight days or until revascularization. <u>Antiplatelet therapy to support PCI after fibrinolytic therapy</u>

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	• After PCI, aspirin should be continued indefinitely. • Clopidogrel should be provided as a 300 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy; a 600 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy; and a dose of 75 mg daily should be given after PCI. • After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses. • Prasugrel, in a 60 mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent. • Prasugrel, in a 10 mg daily maintenance dose, is reasonable after PCI. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. <u>Anticoagulant therapy to support PCI after fibrinolytic therapy</u> • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with IV UFH, additional boluses of IV UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior eight hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between eight and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given.
American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[18]**	<u>Early hospital care- standard medical therapies</u> • Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. • Anti-ischemic and analgesic medications o Nitrates ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral beta-blocker therapy should be initiated within the first 24 hours

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	in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue beta-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to beta-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of beta-clockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when beta-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely

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	NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa

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	inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12

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	months.
	• Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS
	  ○ The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding.
	  ○ Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.

American Heart Association/American College of Cardiology/American College of Clinical Pharmacy/American Society for Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With Chronic Coronary Disease (2023)**[19]	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT)

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	consisting of aspirin and clopidogrel for six months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to three years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. • In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to one month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy.

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	• In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.
European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)**[20]	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u> • The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events. • Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention. • It is recommended to educate patients about the disease, risk factors and treatment strategy. • It is indicated to review the patient's response soon after starting therapy. • Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding. • Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9

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	inhibitor is recommended • ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events • Angina/ischemia relief: o Short-acting nitrates are recommended. o First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. • Event prevention: o Low-dose aspirin daily is recommended in all stable CAD patients. o Clopidogrel is indicated as an alternative in case of aspirin intolerance. o Statins are recommended in all stable CAD patients. o It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes). <u>Treatment in patients with microvascular angina</u> • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • ß-blockers are recommended as a first-line treatment. • Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT). • Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only. • Platelet function testing or genetic testing may be considered in specific or high-risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high-risk situations of

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	elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low-risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low. • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months. <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk. • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
The American College of Cardiology/ American Heart Association: **Practice Guidelines for the Management of Patients with Peripheral Artery Disease (2013)**[21]	<u>Exercise and lower extremity peripheral artery disease (PAD) rehabilitation</u> • A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. • Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times/week for a minimum of 12 weeks. • The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication. <u>Smoking cessation</u> • Patients who are smokers or former smokers should be asked about status of tobacco use at every visit. Patients with lower extremity PAD who use tobacco should be advised to stop smoking. • Patients should be provided with counseling and assistance with developing a plan for smoking cessation. • One or more of the following pharmacological therapies should be offered if not contraindicated: varenicline, bupropion and nicotine replacement therapy. <u>Antiplatelet and antithrombotic drugs</u>

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	• Antiplatelet therapy is indicated to reduce the risk of MI, stroke and vascular death in patients with symptomatic atherosclerotic lower extremity PAD and in asymptomatic patients with ankle brachial index ≤0.90. The usefulness of antiplatelet therapy is not well established in asymptomatic patients with ankle brachial index between 0.91 and 0.99. • Aspirin (75 to 325 mg/day) is recommended to reduce the risk of cardiovascular events. Clopidogrel (75 mg/day) is recommended as an alternative to aspirin. • Combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD who are at high cardiovascular risk and not at increased risk of bleeding. • The addition of warfarin to antiplatelet therapy is of no proven benefit and is potentially harmful due to increased risk of major bleeding. <u>Medical and pharmacological treatment for claudication</u> • Cilostazol (100 mg orally twice daily) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure). • A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure). • Pentoxifylline (400 mg three times daily) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication. • The clinical effectiveness of pentoxifylline as therapy for intermittent claudication is marginal and not well established. • The effectiveness of L-arginine for patients with intermittent claudication is not well established. • The effectiveness of propionyl L-carnitine as a therapy to improve walking distance in patients with intermittent claudication is not well established. • The effectiveness of ginkgo biloba as a therapy to improve walking distance in patients with intermittent claudication is not well established. • Oral vasodilator prostaglandins such as beraprost* and iloprost are not effective medications to improve walking distance in patients with intermittent claudication. • Vitamin E is not recommended as a treatment for patients with intermittent claudication. • Chelation (e.g. ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects.
American College of Cardiology/American Heart Association: **Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease (2016)**[22]	<u>Recommendations for Antiplatelet Agents:</u> • Antiplatelet therapy with aspirin alone (range 75 to 325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce myocardial infarction (MI), stroke, and vascular death in patients with symptomatic peripheral artery disease (PAD). • In asymptomatic patients with PAD (Ankle Brachial Index (ABI) ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death. • In asymptomatic patients with borderline ABI (0.91 to 0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain. • The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established. • DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity

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	revascularization. • The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain. <u>Recommendations for Statin Agents:</u> • Treatment with a statin medication is indicated for all patients with PAD. <u>Recommendations for Antihypertensive Agents:</u> • Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. • The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD. <u>Recommendations for Smoking Cessation:</u> • Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit. • Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program. • Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places. <u>Recommendations for Glycemic Control:</u> • Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team. • Glycemic control can be beneficial for patients with critical limb ischemia (CLI) to reduce limb-related outcomes. <u>Recommendations for Oral Anticoagulation:</u> • The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain. • Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD. <u>Recommendations for Cilostazol:</u> • Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication. <u>Recommendations for Pentoxifylline:</u> • Pentoxifylline is not effective for treatment of claudication.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2021)[23]**	<u>Recommendations for Nonvalvular Atrial Fibrillation:</u> • For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (~30 days) for AF is reasonable within six months of the index event. • VKA therapy, apixaban, dabigatran and rivaroxaban are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. o Selection of agent should be individualized based on risk factors, cost, tolerability, patient preference, drug interactions and other characteristics including renal function and time in INR therapeutic range if the patient has been taking VKA therapy. • Target INR for patients with ischemic stroke or TIA with paroxysmal

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	(intermittent), persistent or permanent AF on VKA therapy is 2.5 (range 2.0 to 3.0).
	• Combination oral anticoagulation (warfarin or a newer agent) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA.
	  o Combination therapy is reasonable in patients with clinically apparent coronary artery disease particularly an acute coronary syndrome or stent placement.
	• For patients with ischemic stroke or TIA and AF who unable to take oral anticoagulants, aspirin alone is recommended.
	  o Adding clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable.
	• For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms.
	• In the presence of high risk for hemorrhagic conversion, it is reasonable to delay initiation of oral anticoagulation beyond 14 days.
	• For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent) is reasonable, depending on perceived risk for thromboembolism and bleeding.
	• The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain.
	
	<u>Recommendations for Acute MI and LV Thrombus:</u>
	• Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months is recommended in most patients with ischemic stroke or TIA in this setting.
	  o Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the American College of Chest Physicians.
	• Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging.
	• In patients with stroke or TIA and new LV thrombus (<3 months), the safety of anticoagulation with a direct oral anticoagulant to reduce risk of recurrent stroke is uncertain.
	• In patients with stroke or TIA in the setting of acute anterior MI with reduced ejection fraction <50% but not evidence of LV thrombus, empirical anticoagulation for at least 3 months might be considered to reduce the risk of recurrent cardioembolic stroke
	
	<u>Recommendations for Cardiomyopathy:</u>
	• In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus, anticoagulant therapy with a VKA is recommended for ≥3 months.
	• In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) and aspirin is reasonable in the absence of major contraindications.
	• In patients with ischemic stroke or TIA in the setting of LV noncompaction, treatment with VKA therapy can be beneficial to reduce the risk of recurrent stroke.
	• In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy

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	without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized. • In patients with stroke or TIA and LVADs, treatment with dabigatran instead of warfarin for the primary or secondary prevention of ischemic stroke or TIA causes harm. <u>Recommendations for Mitral Stenosis, Mitral Regurgitation, Mitral Prolapse, Mitral Annular Calcification, and Aortic Valve Disease</u>: • In patients with VHD (except moderate to severe mitral stenosis or a mechanical heart valve), ischemic stroke or TIA, and AF, DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin therapy. • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with INR target of 2.5 (range, 2.0 to 3.0) is recommended. • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (e.g., carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered instead of antiplatelet therapy. • For patients with rheumatic mitral valve disease who are prescribed VKA therapy after an ischemic stroke or TIA, antiplatelet therapy should not be routinely added. • For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered. • For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended. • For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification. • For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse. <u>Recommendations for Prosthetic Heart Valves:</u> • For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0 to 3.0). • For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5 to 3.5). • For patients with a mechanical aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/day to VKA therapy is recommended. • For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/day or increasing the target INR, depending on bleeding risk. • For patients with a bioprosthetic aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and no other indication for anticoagulation therapy beyond three to six months form the valve placement, long-term therapy with aspirin 75 to 100 mg/day is recommended in preference to long-term anticoagulation. • For patients with a bioprosthetic aortic or mitral valve who have a TIA,

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	ischemic stroke, or systemic embolism despite antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered. <u>Recommendations for Noncardioembolic Stroke or TIA</u>: • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. • Aspirin (50 to 325 mg/day) monotherapy, clopidogrel 75 mg daily, or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. • Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole. This recommendation also applies to patients who are allergic to aspirin. • For patients with recent minor noncardioembolic ischemic stroke or high-risk TIA, DAPT (aspirin plus clopidogrel) should be initiated within 12 to 24 hours of symptom onset and at least within seven days of onset. Therapy should be continued for 21 to 90 days, followed by single agent platelet therapy to reduce the risk of recurrent stroke. • For patients with recent minor to moderate stroke, high-risk TIA< or symptomatic intracranial or extracranial ≥30% stenosis of an artery, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke, but may also increase the risk of serious bleeding events. • The selection of an antiplatelet agent should be individualized on the basis of patient risk facto profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics. • The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for two to three years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA). • For patients who have an ischemic stroke or TIA while taking aspirin, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established. • For patients with a history of ischemic stroke or TIA, AF and coronary artery disease, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet or VKA therapy. • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. • The continued use of DAPT (aspirin plus clopidogrel) for >90 days or the use of triple antiplatelet therapy is associated with excess risk of hemorrhage.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)**[24]	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient

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	risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk

Clinical Guideline	Recommendations
	reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable.

Clinical Guideline	Recommendations
	Recommendations for treatment of tobacco use • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. Recommendations for aspirin use • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the oral anticoagulants 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 Oral Anticoagulants[1-5,7-8]

Indication	Apixaban	Dabigatran	Edoxaban§	Rivaroxaban	Warfarin
Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement					✔
Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism					✔
Prophylaxis of deep vein thrombosis and pulmonary embolism in patients who have undergone hip replacement surgery		✔			
Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery	✔			✔	
Prophylaxis of venous thromboembolism (VTE) and VTE related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and				✔	

Indication	Apixaban	Dabigatran	Edoxaban§	Rivaroxaban	Warfarin
other risk factors for VTE and not at high risk of bleeding					
Reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction					✔
Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	✔	✔	✔	✔ *	
Treatment of deep vein thrombosis and pulmonary embolism	✔	✔ †	✔ †	✔	
Treatment of venous thromboembolic events in pediatric patients 8 to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days		✔			
Treatment of VTE in pediatric patients aged 3 months to less than 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days		✔ (pellet)			
Reduce the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial therapy	✔	✔		✔ ‡	
Reduce the risk of recurrence of venous thromboembolic events in pediatric patients 8 to less than 18 years of age who have been previously treated		✔			
Reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated		✔ (pellet)			
Treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years of age				✔	
Reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) in patients with coronary artery disease when given in combination with aspirin				✔	
Reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in patients with peripheral artery disease (PAD), including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD when given in combination with aspirin				✔	
Thromboprophylaxis in pediatric patients 2 years of age and older with congenital heart disease after the Fontan procedure				✔	

*There is limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.
†Indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days.
‡Indicated to reduce the risk of recurrent DVT or PE following initial six months of treatment for DVT/PE.
§ Edoxaban should not be used in patients with CrCl >95 mL/min because of an increased risk of ischemic stroke compared to warfarin.

IV. Pharmacokinetics

The pharmacokinetic parameters of the oral anticoagulants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Oral Anticoagulants[1-5,8]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Apixaban	50	27	None	6.8 to 12
Dabigatran	3 to 7	80*	Dabigatran (major); 1-, 2-, 3-, 4-O-acylglucuronide (all minor)	12 to 17
Edoxaban	62	50	M-4 (<10% exposure of edoxaban)	10 to 14
Rivaroxaban	66 to 100, dose-dependent	66	None	5 to 11.7
Warfarin	~100	92	Warfarin alcohols	168

*Intravenous administration.

V. Drug Interactions

Major drug interactions with the oral anticoagulants are listed in Table 5.

Table 5. Major Drug Interactions with the Oral Anticoagulants[8]

Generic Name(s)	Interaction	Mechanism
Anticoagulants (Apixaban, Dabigatran, Edoxaban, Rivaroxaban, Warfarin)	NSAIDs	The risk of bleeding may be increased. Increased anticoagulant activity and risk of bleeding gastric irritation and decreased platelet function contribute.
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Warfarin)	Azole antifungals	Effect of anticoagulant may be increased.
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Warfarin)	Macrolide antibiotics	The anticoagulant effect of oral anticoagulants may be increased. Inhibition of metabolism (CYP3A4) and P-gp by certain macrolide and related antibiotics may increase exposure.
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Edoxaban, Warfarin)	Rifamycins	Increased elimination of anticoagulants due to induction of metabolism (CYP3A4) and P-gp transport by rifamycins.
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Warfarin)	St. John's Wort	Increased elimination of anticoagulants due to induction of metabolism (CYP3A4) and P-gp transport by St. John's Wort.
Anticoagulants (Apixaban, Dabigatran, Edoxaban, Rivaroxaban, Warfarin)	Antiplatelet agents	Concurrent use may result in increased risk of bleeding.

Generic Name(s)	Interaction	Mechanism
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Warfarin)	Fibric acids	Concurrent use of fenofibrate and anticoagulants may result in enhanced anticoagulant effect.
Anticoagulants (Apixaban, Dabigatran, Edoxaban, Rivaroxaban, Warfarin)	Serotonin reuptake inhibitors	Concurrent use may result in an increased risk of bleeding.
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Warfarin)	Nintedanib	Concurrent use of nintedanib and anticoagulants may result in increased risk of bleeding.
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban)	Hydantoins	Increased elimination of apixaban due to induction of metabolism (CYP3A4) and P-gp transport by certain hydantoins.
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Warfarin)	Protease Inhibitors	Inhibition of metabolism (CYP3A4) and P-gp by certain protease inhibitors increases apixaban exposure.
Anticoagulants (Apixaban, Dabigatran, Rivaroxaban, Warfarin)	Carbamazepine	Increased elimination of apixaban due to induction of metabolism (CYP3A4) and P-gp transport by carbamazepine.
Warfarin	Androgens (17-alkyl)	The hypoprothrombinemic effect of oral anticoagulants is potentiated by 17-alkyl androgens.
Warfarin	Antineoplastic Agents (Capecitabine, carboplatin, cisplatin, cyclophosphamide, etoposide, fluorouracil, gemcitabine, paclitaxel)	The anticoagulant effect of warfarin may be increased due to possible protein displacement, inhibition of warfarin metabolism, or inhibition of clotting-factor synthesis.
Warfarin	Barbiturates	Barbiturates reduce the effects of anticoagulants due to increased metabolic clearance of anticoagulants, likely caused by induction of hepatic microsomal enzymes.
Warfarin	Cephalosporins	The anticoagulant effect of warfarin is increased.
Warfarin	Quinine derivatives	Quinine derivatives may inhibit the hepatically synthesized clotting factors. Anticoagulation may be potentiated.
Warfarin	Quinolones	Increased anticoagulant effect of warfarin.
Warfarin	Sulfonamides	The anticoagulant effect of warfarin may be enhanced.
Warfarin	Tetracyclines	The action of warfarin may be increased.
Warfarin	Thioamines (Methimazole, Propylthiouracil)	The action of oral anticoagulants may be changed during coadministration of thioamines.
Warfarin	Alteplase	Risk of serious bleeding may be increased due to additive or synergistic effects.
Warfarin	Amiodarone	Amiodarone inhibits the metabolism (CYP1A2, CYP2C9) of the R- and S-enantiomers of warfarin.

Generic Name(s)	Interaction	Mechanism
		Hypoprothrombinemic effect of oral anticoagulants is augmented by concomitant amiodarone therapy.
Warfarin	Cimetidine	Stereoselective inhibition of the hepatic metabolism of the less potent (R)-warfarin enantiomer increase in warfarin effects; possible hemorrhage.
Warfarin	Dextrothyroxine	Dextrothyroxine increases the hypoprothrombinemic effect of oral anticoagulants.
Warfarin	Metronidazole	Liver metabolism of the S- enantiomorph of racemic warfarin may be decreased by metronidazole.
Warfarin	Tamoxifen	The hypoprothrombinemic effect of oral anticoagulants may be increased, possibly with bleeding.
Warfarin	Vitamin E	Vitamin E may interfere with vitamin K–dependent clotting factors, thereby adding to the effects of oral anticoagulants.
Warfarin	Corticosteroids	Corticosteroids may reduce anticoagulant dose requirements and occasionally induce hypercoagulation that could oppose anticoagulant action.
Warfarin	HMG-CoA Reductase Inhibitors (fluvastatin, lovastatin, rosuvastatin, simvastatin)	The anticoagulant effect of warfarin may increase. Decreased S- and R-warfarin clearance by inhibition of CYP2C9 and CYP3A4 metabolism, respectively.
Warfarin	Hydantoins	Increased hydantoin serum concentrations with possible toxicity. Increased PT and an increased risk of bleeding may occur.
Warfarin	Penicillins	Large IV doses of penicillins can increase the bleeding risks of anticoagulants by prolonging bleeding time. Conversely, nafcillin and dicloxacillin have been associated with warfarin resistance, which may persist for three weeks or more following discontinuation of the antibiotic.
Warfarin	Thiopurines (Azathioprine, Mercaptopurine)	Thiopurines have been reported to increase the synthesis or activation of prothrombin, as well as reduce plasma warfarin concentrations.
Warfarin	Acetaminophen	Acetaminophen (APAP) appears to increase the antithrombotic effect of oral anticoagulants in a dose-dependent manner. The interaction may not be clinically important with low-dose, infrequent use of APAP.
Warfarin	Aminoglutethimide	Increased warfarin metabolic clearance, probably because of liver microsomal enzyme induction. Warfarin's action to decrease prothrombin levels may be reduced.
Warfarin	Argatroban	Both warfarin and argatroban increase the INR, increasing the risk of bleeding.
Warfarin	Bosentan	The effects of warfarin may be decreased. Induction of warfarin metabolism (CYP2C9 and CYP3A4) by bosentan is suspected.
Warfarin	Chloramphenicol	Anticoagulation action of oral anticoagulants may be enhanced by chloramphenicol due to possible inhibition of hepatic metabolism of oral anticoagulants.
Warfarin	Cholestyramine	The anticoagulant effect of oral anticoagulants may be decreased by cholestyramine due to reduced oral anticoagulant absorption and possibly increased elimination.
Warfarin	Clopidogrel	The risk of nonfatal and fatal bleeding may be increased with combined therapy.
Warfarin	Disulfiram	Disulfiram may increase the anticoagulant effects of warfarin.
Warfarin	Dronedarone	The anticoagulant effect of warfarin is increased.

Generic Name(s)	Interaction	Mechanism
Warfarin	Gefitinib	The anticoagulant effect of warfarin may be potentiated, increasing the risk of bleeding.
Warfarin	Glucagon	The anticoagulant effect of warfarin may be enhanced in patients receiving sustained doses of glucagon (bleeding may occur).
Warfarin	Glutethimide	Glutethimide appears to increase the clearance of coumarin anticoagulants by stimulation of hepatic microsomal enzymes.
Warfarin	Griseofulvin	The anticoagulant activity of warfarin may be decreased.
Warfarin	Nevirapine	Induction of warfarin metabolism (CYP2C9) by nevirapine is suspected.
Warfarin	Tramadol	The effect of the oral anticoagulant may be increased.
Warfarin	Trazodone	The hypoprothrombinemic effect of warfarin may be decreased. Suboptimal anticoagulation with possible exacerbation of the disease being treated may occur.
Warfarin	Vitamin K	Vitamin K may inhibit the effect of warfarin on vitamin K–dependent clotting factors.

VI. Adverse Drug Events

The most common adverse drug events reported with the oral anticoagulants are listed in Table 6. The boxed warning for apixaban, dabigatran, and rivaroxaban is included in Table 7, edoxaban in Table 8, and warfarin in Table 9.

Table 6. Adverse Drug Events (%) Reported with the Oral Anticoagulants[7]

Adverse Event	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Abdominal pain	-	✔	-	2	✔
Alopecia	-	-	-	-	✔
Anemia	3	1 to 4	2	3	-
Back pain	-	-	-	4	-
Bloating	-	-	-	-	✔
Bruising	1 to 2	-	-	-	-
Chills	-	-	-	-	✔
Cholestatic hepatitis	-	-	-	-	✔
Cholesterol microemboli	-	-	-	-	✔
Confusion		-	-	-	-
Dermatitis	-	-	-	-	✔
Diarrhea	-	-	-	-	✔
Dizziness	-	-	-	2	-
Dyspepsia	-	8	-	1	-
Elevated liver enzymes	≤1	2 to 3	-	-	✔
Epistaxis	≤4	-	5	-	-
Fatigue	-	-	-	1	-
Flatulence	-	-	-	-	✔
Gastrointestinal symptoms	-	25 to 40	-	-	-
GERD	-	✔	-	✔	-
Hematuria	≤2	-	≤2	-	-
Hemoptysis	≤1	-	-	-	-
Hemorrhage	1 to 12	11 to 19	22	5 to 28	✔
Hepatic function abnormal	-	-	5 to 8	-	-
Hepatitis	-	-	-	-	✔
Hypermenorrhea	1	-	-	-	-
Hypersensitivity/allergic	✔	✔	-	✔	✔

Adverse Event	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
reactions					
Hypotension	✔	-	-	-	-
Insomnia	-	-	-	2	-
Increased Gamma-Glutamyl Transferase	≤1	-	-	-	-
Increased serum transaminases	≤1	-	-	2	-
Infection, sinusitis or urinary tract infection	-	-	-	✔	-
Myocardial infarction, fatal and non-fatal	-	✔	-	-	-
Nausea	3	-	-	1 to 3	✔
Necrosis of the skin	-	-	-	-	✔
Oropharyngeal pain	-	-	-	1	-
Osteoarthritis	-	-	-	2	-
Pruritus	-	-	-	2	✔
Rash	✔	-	4	-	✔
Syncope	-	-	-	1	-
Systemic atheroemboli	-	-	-	-	✔
Taste perversion	-	-	-	-	✔
Toothache	-	-	-	1	-
Tracheal or tracheobronchial calcification	-	-	-	-	✔
Ulcer, gastrointestinal	-	✔	-	-	-
Vomiting	-	-	-	-	✔

✔ Percent not specified.
- Event not reported.

Table 7. Boxed Warning for Apixaban, Rivaroxaban, and Dabigatran[1,2,4]

WARNING
(A) Premature discontinuation of any oral anticoagulant, including Pradaxa, Xarelto, and Eliquis increases the risk of thrombotic events. If anticoagulation is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant. (B) Epidural or spinal hematomas may occur in patients treated with oral anticoagulants who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include: -Use of indwelling epidural catheters -Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants -History of traumatic or repeated epidural or spinal punctures -History of spinal deformity or spinal surgery -Optimal timing between the administration of oral anticoagulants and neuraxial procedures is not known Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

Table 8. Boxed Warning for Edoxaban[3]

WARNING
WARNING: REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) >95 ML/MIN; PREMATURE DISCONTINUATION OF

EDOXABAN INCREASES THE RISK OF ISCHEMIC EVENTS; SPINAL/EPIDURAL HEMATOMA

Reduced efficacy in nonvalvular atrial fibrillation patients with CrCl >95 ml/min

- Edoxaban should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used.

Premature discontinuation of edoxaban increases the risk of ischemic events

- Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If edoxaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance.

Spinal/epidural hematoma

- Epidural or spinal hematomas may occur in patients treated with edoxaban who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
  - use of indwelling epidural catheters
  - concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
  - a history of traumatic or repeated epidural or spinal punctures
  - a history of spinal deformity or spinal surgery
  - optimal timing between the administration of edoxaban and neuraxial procedures is not known
- Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
- Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

Table 9. Boxed Warning for Warfarin[5]

WARNING
Bleeding risk: Warfarin can cause major or fatal bleeding. Perform regular monitoring of international normalized ratio (INR) on all treated patients. Drugs, dietary changes, and other factors affect INR levels achieved with warfarin therapy. Instruct patients about prevention measures to minimize the risk of bleeding and to report immediately to their health care provider signs and symptoms of bleeding.

VII. Dosing and Administration

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

Table 10. Usual Dosing Regimens for the Oral Anticoagulants[1-5,7,8]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Apixaban	<u>Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation:</u> Tablet: 5 mg BID; 2.5 mg BID in patients with at least two of the following characteristics- age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL <u>Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery:</u>	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg Starter pack: 74 tablets of 5 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: 2.5 mg BID for 12 days (knee) or 35 days (hip) Treatment of deep vein thrombosis and pulmonary embolism: Tablet: 10 mg BID for 7 days, followed by 5 mg BID Reduce the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial therapy‡: Tablet: 2.5 mg BID		
Dabigatran	Prophylaxis of deep vein thrombosis and pulmonary embolism in patients who have undergone hip replacement surgery: Capsule: 110 mg taken one to four hours post-surgery, then 220 mg QD for 28 to 35 days Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: Capsule: 150 mg BID Treatment of deep vein thrombosis and pulmonary embolism†: Capsule: 150 mg BID Reduce the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial therapy: Capsule: 150 mg BID	Treatment of venous thromboembolic events† in pediatric patients 8 to less than 18 years of age: Capsule: weight-based dosing from 75 to 260 mg BID, see prescribing information for details Treatment of VTE in pediatric patients aged 3 months to less than 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days: Oral pellets: age and weight-based dosing from 30 mg to 260 mg BID, see prescribing information for details Reduce the risk of recurrence of venous thromboembolic events in pediatric patients 8 to less than 18 years of age who have been previously treated: Capsule: weight-based dosing from 75 to 260 mg BID, see prescribing information for details Reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who	Capsule: 75 mg 110 mg 150 mg Pellet pack: 20 mg 30 mg 40 mg 50 mg 110 mg 150 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		have been previously treated: Oral pellets: age and weight-based dosing from 30 mg to 260 mg BID, see prescribing information for details	
Edoxaban	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: Tablet: 60 mg QD Treatment of deep vein thrombosis and pulmonary embolism†: Tablet: 60 mg QD	Safety and efficacy have not been established in pediatric patients.	Tablet: 15 mg 30 mg 60 mg
Rivaroxaban	Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery: Tablet: 10 mg QD for 12 days (knee) or 35 days (hip) Prophylaxis of venous thromboembolism in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding: Tablet: 10 mg once daily, in hospital and after hospital discharge, for a total recommended duration of 31 to 39 days Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation*: Tablet: 20 mg QD Treatment of deep vein thrombosis and pulmonary embolism: Tablet: initial, 15 mg BID for the first 21 days; maintenance, 20 mg QD Reduce the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial therapy‡: Tablet: 10 mg QD Reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) in patients with coronary artery disease when given in combination with aspirin: Tablet: 2.5 mg BID, plus aspirin QD Reduce the risk of major thrombotic vascular events in peripheral artery disease, including patients after lower extremity revascularization due to symptomatic peripheral artery disease when given in combination with aspirin: Tablet: 2.5 mg BID, plus aspirin QD	Treatment of venous thromboembolism and reduction in risk of recurrent venous thromboembolism in pediatric patients birth to less than 18 years of age: Suspension, tablet: weight-based dosing from 0.8 mg TID to 20 mg QD, see prescribing information for details Thromboprophylaxis in pediatric patients with congenital heart disease after the Fontan procedure: Suspension, tablet: weight-based dosing from 1.1 mg BID to 10 mg QD, see prescribing information for details	Tablet: 2.5 mg 10 mg 15 mg 20 mg Starter Pack: 42 tablets of 15 mg and 9 tablets of 20 mg Suspension: 1 mg/mL
Warfarin	Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation	Safety and efficacy in children have not been	Tablet: 1 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	and/or cardiac valve replacement: Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; maintain an INR of 2.0 to 3.0 Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism: Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; treat for six to 12 months or indefinitely Reduce the risk of death, recurrent myocardial infarction and thromboembolic events such as stroke or systemic embolization after myocardial infarction: Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; maintain an INR of 3.0 to 4.0 (high intensity) or of 2.0 to 3.0 (moderate intensity)	established.	2 mg 2.5 mg 3 mg 4 mg 5 mg 6 mg 7.5 mg 10 mg

BID=twice-daily, INR=International Normalized Ratio, QD=once-daily
*There is limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.
†Indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days.
‡Indicated to reduce the risk of recurrent DVT or PE following initial six months of treatment for DVT/PE.

VIII. Effectiveness

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

Table 11. Comparative Clinical Trials with the Oral Anticoagulants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Reducing the Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation				
Connolly et al.[25] (2011) AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	AC, DB, MC, PG, RCT Patients ≥50 years of age with AF for at least six months before enrollment or documented by 12-lead ECG on the day of screening and at least one of the following risk factors: prior stroke or TIA, age ≥75, arterial hypertension, diabetes mellitus, heart failure (NYHA Class ≥2), a LVEF ≤35%, or peripheral artery disease Patients could not be receiving VKA therapy because it had already been unsuitable for them or was expected to be unsuitable.	N=5,599 1.1 years	Primary: Incidence of stroke (ischemic or hemorrhagic) or systemic embolism and major bleeding Secondary: Rates of MI, death from vascular causes, death from any cause and composite of major vascular events	Primary: The incidence of stroke or systemic embolism was significantly lower in patients randomized to receive treatment with apixaban compared to treatment with aspirin (1.6 vs 3.7% per year; HR, 0.45; 95% CI, 0.32 to 0.62; P<0.001). The incidence of ischemic stroke was significantly lower in the apixaban treatment group (1.1 vs 3.0% per year; HR, 0.37; 95% CI, 0.25 to 0.55; P<0.001); however, there was no difference between the groups with regard to hemorrhagic stroke (0.2 vs 0.3% per year, respectively; HR, 0.67; 95% CI, 0.24 to 1.88; P=0.45). There was no statistically significant difference in the incidence of major bleeding in the apixaban treatment group compared to the aspirin treatment group (1.4 vs 1.2% per year, respectively; HR, 1.13; 95% CI, 0.74 to 1.75; P=0.57). The incidences of intracranial bleeding (0.4 vs 0.4% per year; P=0.69), extracranial bleeding (1.1 vs 0.9% per year; P=0.42), gastrointestinal bleeding (0.4 vs 0.4% per year; P=0.71), nongastrointestinal bleeding (0.6 vs 0.4% per year; P=0.22) and fatal bleeding (0.1 vs 0.2% per year; P=0.53) were not significantly different between the apixaban and aspirin treatment groups. Secondary: The incidence of MI was similar between the apixaban and aspirin treatment groups (0.8 vs 0.9% per year, respectively; HR, 0.86; 95% CI, 0.50 to 1.48; P=0.59). The incidence of death from vascular causes (2.7 vs 3.1% per year, respectively; HR, 0.87; 95% CI, 0.65 to 1.17; P=0.37) or death from any cause (3.5 vs 4.4% per year; HR, 0.79; 95% CI, 0.62 to 1.02; P=0.07) was not significantly different between patients receiving apixaban or aspirin. The composite rate of stroke, systemic embolism, MI, death from vascular

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				causes or major bleeding was significantly lower in the apixaban group compared to the aspirin group (ITT, 5.3 vs 7.2% per year; HR, 0.74; 95% CI, 0.60 to 0.90; P=0.003; on-treatment analysis, 4.0 vs 6.3% per year; HR, 0.64; 95% CI, 0.51 to 0.80; P<0.001). Treatment with apixaban significantly reduced the incidence of hospitalization for cardiovascular causes compared to treatment with aspirin (12.6 vs 15.9% per year; HR, 0.79; 95% CI, 0.69 to 0.91; P<0.001). The rate of clinically relevant nonmajor bleeding (3.1 vs 2.7% per year; HR, 1.15; 95% CI, 0.86 to 1.54; P=0.35) and minor bleeding (6.3 vs 5.0% per year; HR, 1.24; 95% CI, 1.00 to 1.53; P=0.50) was similar between the apixaban and aspirin treatment groups.
Diener et al.[26] (2012) AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of AVERROES[18] Patients enrolled in the AVERROES trial stratified based on previous stroke and TIA	N=5,599 1.1 years	Primary: Incidence of stroke (ischemic or hemorrhagic) or systemic embolism and major bleeding Secondary: Rates of MI, death from vascular causes, death from any cause and composites of major vascular events	Primary: The incidence of stroke or systemic embolism was significantly lower in patients with no previous stroke or TIA compared to patients with a history of stroke or TIA (2.36 vs 5.73% per year; HR, 2.38; 95% CI, 1.66 to 3.34; P<0.0001). There was a significantly lower incidence of stroke or systemic embolism with apixaban treatment compared to aspirin treatment in those without previous stroke or TIA (HR, 0.51; 95% CI, 0.35 to 0.74) and in those with a previous stroke or TIA (HR; 0.29; 95% CI, 0.15 to 0.60); however, the difference between the groups was not statistically significant (P=0.17). The incidence of major bleeding was not significantly different between the apixaban and aspirin treatment groups, regardless of previous stroke or TIA history (P=0.73). Secondary: There was no significant difference between apixaban and aspirin treatment with regard to the incidence of MI. Moreover, the difference in MI between patients with a history of stroke or TIA and those without a history of stroke or TIA was not statistically significant (P=0.33). There was no significant difference between the apixaban and aspirin treatment groups in the incidence of death from vascular causes, regardless of previous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				stroke history (P=0.79). There was no statistically significant difference between the apixaban and aspirin treatment groups with regard to the incidence of stroke (P=0.26), ischemic or unspecified stroke (P=0.36), hemorrhagic stroke (P=0.25), disabling or fatal stroke (P=0.32) or death from any cause (P=0.89) between patients with and without a prior history of stroke or TIA. Similarly, no significant differences in intracranial bleeding (P=0.92), extracranial or unclassified bleeding (P=0.49) or gastrointestinal bleeding (P=0.89) were observed between the groups with regard to prior stroke or TIA history.
Flaker et al.[27] (2012) AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of AVERROES[18] Patients enrolled in the AVERROES trial who experienced bleeding during the treatment period	N=5,599 1.1 years	Primary: Major bleeding and clinically relevant nonmajor bleeding Secondary: Not reported	Primary: There were 44 major hemorrhages in the apixaban group and 39 in the aspirin group. There were 96 clinically relevant nonmajor hemorrhages in the apixaban group and 84 in the aspirin group. Three patients in the apixaban group and seven patients in the aspirin group had both severities of bleeding. There was a similar incidence of major bleeding (HR, 1.13; 95% CI, 0.74 to 1.75; P=0.57), clinically relevant nonmajor bleeding (HR, 1.15; 95% CI, 0.86 to 1.54; P=0.35) and major or clinically relevant nonmajor bleeding (HR, 1.18; 95% CI, 0.92 to 1.51; P=0.19) between the apixaban and aspirin treatment groups. Of patients who experienced bleeding during the treatment with apixaban and aspirin, respectively, the incidence of major intracranial bleeding (0.35 vs 0.41% per year; P=0.69), gastrointestinal bleeding (0.35 vs 0.45% per year; P=0.56), and surgical or trauma bleeding (0.19 vs 0.16% per year; P=0.75) was not significantly different between the groups. With regard to major or clinically relevant nonmajor bleeding, there was no statistically significant difference between apixaban and aspirin at any site of bleeding (P>0.05 for all). The independent predictors of major and clinically relevant nonmajor bleeding that were significantly different between those treated with apixaban and aspirin were the use of nonstudy aspirin >50% of the time (P=0.02 for both treatments)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and a history of daily/occasional nosebleeds (P=0.02 and P=0.01, respectively). There were no significant differences in major and clinically relevant nonmajor bleeding when patients were stratified by age, sex, body mass index, study dose of aspirin, or estimated glomerular filtration rate (P values not reported). Secondary: Not reported
Granger et al.[28] (2011) ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	AC, DB, DD, MC, NI, RCT Patients with AF or flutter at baseline or two or more episodes of AF or flutter, as documented by ECG at least two weeks apart in the 12 months before enrollment and at least one of the following risk factors for stroke age ≥75, previous stroke, TIA, systemic embolism, symptomatic heart failure within previous three months or LVEF ≤40% and diabetes mellitus or hypertension requiring treatment	N=18,201 1.8 years	Primary: Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: Death from any cause, rate of MI, composite of stroke, systemic embolism or death from any cause, composite of stroke, systemic embolism, MI or death from any cause, composite of PE or DVT, major bleeding or clinically relevant nonmajor bleeding, any bleeding and	Primary: Stroke or systemic embolism occurred in 212 patients treated with apixaban and 265 patients treated with warfarin (1.27 vs 1.60% per year, respectively; HR, 0.79; 95% CI, 0.66 to 0.95; P<0.001 for non-inferiority and P=0.01 for superiority). Treatment with apixaban significantly lowered the incidence of hemorrhagic stroke compared to treatment with warfarin (0.24 vs 0.47% per year; HR, 0.51; 95% CI, 0.35 to 0.75; P<0.001). There was no statistically significant difference between the apixaban and warfarin treatment groups with regard to a reduction in ischemic or uncertain type of stroke (0.97 vs 1.05% per year, respectively; HR, 0.92; 95% CI, 0.74 to 1.13; P=0.42) or systemic embolism (0.09 vs 0.10% per year, respectively; HR, 0.87; 95% CI, 0.44 to 1.75; P=0.70). There was a significantly lower incidence of major bleeding associated with apixaban treatment compared to warfarin treatment (2.13 vs 3.09% per year; HR, 0.69; 95% CI, 0.60 to 0.80; P<0.001). Apixaban treatment was associated with a significantly lower incidence of major intracranial bleeding (0.33 vs 0.80% per year; HR, 0.42; 95% CI, 0.30 to 0.58; P<0.001), and major bleeding at other locations (1.79 vs 2.27% per year; HR, 0.79; 95% CI, 0.68 to 0.93; P=0.004) compared to warfarin treatment. There was a similar incidence of major gastrointestinal bleeding between the treatment groups (0.76 vs 0.86% per year, respectively; HR, 0.89; 0.70 to 1.15; P=0.37). Secondary: Patients randomized to receive apixaban had a lower incidence of death from any cause (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to 0.998; P=0.047)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse events	compared to patients randomized to warfarin treatment. There was a similar rate of MI between the apixaban and warfarin treatment groups with regard to incidence of MI (0.53 vs 0.61% per year, respectively; HR, 0.88; 95% CI, 0.66 to 1.17; P=0.37). The composite of stroke, systemic embolism, or death from any cause was significantly lower in the apixaban treatment group compared to the warfarin treatment group (4.49 vs 5.04% per year; HR, 0.89; 95% CI, 0.81 to 0.98; P=0.02). Similarly, the composite of stroke, systemic embolism, MI or death from any cause was significantly lower in the apixaban treatment group compared to the warfarin treatment group (4.85 vs 5.49% per year; HR, 0.88; 95% CI, 0.80 to 0.97; P=0.01). The incidence of PE or DVT was similar between the apixaban and warfarin treatment groups (0.04 vs 0.05% per year, respectively; HR, 0.78; 95% CI, 0.29 to 2.10; P=0.63). Apixaban treatment was associated with a significantly lower rate of major or clinically relevant nonmajor bleeding compared to warfarin treatment (4.07 vs 6.01% per year; HR, 0.68; 95% CI, 0.61 to 0.75; P<0.001). Moreover, apixaban reduced GUSTO severe bleeding, GUSTO moderate or severe bleeding, TIMI major bleeding and TIMI major or minor bleeding compared to warfarin (P<0.001 for all). There was a statistically significant reduction in any bleeding in the apixaban treatment group compared to the warfarin treatment group (18.1 vs 25.8% per year; HR, 0.71; 95% CI, 0.68 to 0.75; P<0.001). Adverse events occurred in a similar proportion of patients in the apixaban group and in the warfarin group (81.5 and 83.1%, respectively) as did the proportion of patients who experienced serious adverse events (35.0 and 36.5%, respectively). The rates of liver function abnormalities were similar between the treatment groups.
Easton et al.[29]	Subanalysis of	N=18,201	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2012) ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	ARISTOTLE[21] Patients enrolled in the ARISTOTLE trial stratified based on previous stroke and TIA	1.8 years	Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: Death from any cause, incidence of stroke, hemorrhagic stroke, ischemic or uncertain type of stroke, disabling or fatal stroke, cardiovascular death, intracranial, gastrointestinal and total bleeding	The relative reduction in the risk of stroke or systemic embolism with apixaban compared to warfarin was not significantly different among patients with a history of previous stroke (HR, 0.76; 95% CI, 0.56 to 1.03) and those without (HR, 0.82; 95% CI, 0.65 to 1.03) a previous history of stroke or TIA (P=0.71). Treatment with apixaban significantly reduced the risk of major bleeding compared to warfarin in patients with a history of stroke or TIA (HR, 0.73; 95% CI, 0.55 to 0.98) and patients without a history of stroke or TIA (HR, 0.68; 95% CI, 0.58 to 0.80); however, the difference between the groups was not statistically significant (P=0.69). Secondary: The reduction in death from any cause with apixaban vs warfarin was similar among patients with a history of stroke or TIA (HR, 0.0.89; 95% CI, 0.70 to 1.12) and patients without a stroke or TIA history (HR, 0.90; 95% CI, 0.79 to 1.02; P=0.89). The reduction in the risk of stroke was not significantly different between those with a prior history of stroke or TIA (HR, 0.71; 95% CI, 0.52 to 0.98) and those without a history of stroke or TIA (HR, 0.84; 95% CI, 0.67 to 1.06) who were treated apixaban compared to warfarin (P=0.40). The reduction in the risk of hemorrhagic stroke with apixaban compared to warfarin was similar among patients with a history of stroke or TIA (HR, 0.40; 95% CI, 0.21 to 0.78) and patients without a history of stroke or TIA (HR, 0.59; 95% CI, 0.37 to 0.94; P=0.35). There was no statistically significant difference in the reduction in ischemic or unknown type of stroke with apixaban compared to warfarin among patients with a history of stroke or TIA (HR, 0.86; 95% CI, 0.60 to 1.22) and patients without a stroke or TIA history (HR, 0.97; 95% CI, 0.74 to 1.26; P=0.61). The reduction in disabling or fatal stroke with apixaban compared to warfarin was similar among patients with a history of stroke or TIA (HR, 0.87; 95% CI, 0.57 to 1.34) and patients without a stroke or TIA history (HR, 0.60; 95% CI, 0.41 to 0.86; P=0.18).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The significant reduction in death from any cause with apixaban compared to warfarin was consistent among patients with a history of stroke or TIA (HR, 0.73; 95% CI, 0.55 to 0.98) and patients without a stroke or TIA history (HR, 0.68; 95% CI, 0.58 to 0.80; P=0.69). There was no significant reduction in the risk of total bleeding (P=0.70), intracranial bleeding (P=0.60) or gastrointestinal bleeding (P=0.87) between patients with a previous history of stroke or TIA who received apixaban compared to warfarin and patients without a history of stroke or TIA.
Lopes et al.[30] (2012) ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of ARISTOTLE[21] Patients enrolled in the ARISTOTLE trial stratified based on $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores	N=18,201 1.8 years	Primary: Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: MI, death from any cause, intracranial bleeding, TIMI major or minor bleeding, GUSTO moderate or severe bleeding, any bleeding and net clinical events (stroke or systemic embolism, major bleeding and all-cause mortality)	Primary: Apixaban significantly reduced stroke or systemic embolism with no evidence of a differential effect by risk of stroke ($CHADS_2$ score; P=0.4457, CHA_2DS_2VASc score P=0.1210) or bleeding (HAS-BLED score P=0.9422). Patients treated with apixaban experienced lower rates of major bleeding compared to patients treated with warfarin, with no difference between score categories ($CHADS_2$; P=0.4018, CHA_2DS_2VASc; P=0.2059 and HAS-BLED; P=0.7127). Secondary: Patients treated with apixaban had significantly lower rates of stroke or systemic embolism (P=0.0114), mortality (P=0.0465), major bleeding (P<0.0001), intracranial bleeding (P<0.0001), and any bleeding (P<0.0001) compared to patients receiving warfarin, regardless of $CHADS_2$ score. The benefits of apixaban compared to warfarin for all endpoints across CHA_2DS_2VASc categories were similar to those seen across $CHADS_2$ score categories. There was no difference in the rate of MI between patients in different risk categories. Regardless of HAS-BLED score, patients receiving treatment with apixaban had lower rates of stroke or systemic embolism (P=0.0114), mortality (P=0.0465), major bleeding (P<0.0001), TIMI major or minor bleeding (P<0.0001), GUSTO severe or moderate bleeding (P<0.0001), and any bleeding (P<0.0001) compared to patients treated with warfarin. The reduction in intracranial bleeding with apixaban compared to warfarin was greater in patients with a HAS-BLED score of three or higher (HR, 0.22; 95% CI, 0.10 to 0.48) compared to patients with a HAS-BLED score of less than one (HR, 0.66;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				95% CI, 0.39 to 1.12); however, the difference was not significant (P=0.0604). Irrespective of $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED score, patients randomized to receive treatment with apixaban experienced lower rates of the composite of stroke, systemic embolism, major bleeding, and all-cause mortality compared to patients randomized to warfarin. These results were driven mainly by reductions in bleeding.
Garcia et al.[31] (2013) ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80 years, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of ARISTOTLE[21] Patients enrolled in the ARISTOTLE trial stratified based on previous VKA use	N=18,201 1.8 years	Primary: Composite of all stroke (ischemic or hemorrhagic) and systemic embolism. Secondary: Mortality, major bleeding, intracranial bleeding, and permanent early treatment discontinuation	Primary: Compared with patients in the warfarin arm, patients randomized to receive apixaban had numerically lower rates of stroke/systemic embolism irrespective of prior VKA use. For stroke/systemic embolism, the differences favoring apixaban over warfarin were consistent: the HR was 0.86 (95% CI, 0.67 to 1.11) in the VKA-naive patients and 0.73 (95% CI, 0.57 to 0.95) in the VKA-experienced patients (P=0.39). The treatment effects of apixaban (vs warfarin) were not modified by VKA naivety. Secondary: A similar consistency of treatment effect was seen for other key end points; numerically lower rates of major bleeding and all-cause death were seen in the apixaban treated patients, and there is no evidence that this effect was modified by VKA naivety. Apixaban-treated patients had lower rates of intracranial bleeding overall; the effect of apixaban on intracranial bleeding was less pronounced in patients who were VKA naive (HR, 0.60; 95% CI, 0.38 to 0.93) than in those who were VKA-experienced (HR 0.28; 95% CI, 0.17 to 0.46) (P=0.02). Premature permanent study drug discontinuation was numerically less likely in the patients assigned to apixaban whether they were VKA naive (HR, 0.87; 95% CI, 0.79 to 0.95) or VKA experienced (HR, 0.93; 95% CI, 0.85 to 1.02).
Hylek et al.[32] (2014) ARISTOTLE Apixaban 5 mg	Subanalysis of ARISTOTLE[21] Patients enrolled in the ARISTOTLE	N=18,201 1.8 years	Primary: First major hemorrhage Secondary:	Primary: Major hemorrhage occurred in 789 patients (4.3%) overall; 327 in the apixaban group (2.13% per year) compared with 462 in the warfarin group (3.09% per year; HR 0.69, 95% CI: 0.60 to 0.80; P< 0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80 years, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	trial stratified based on bleeding events		Major extracranial hemorrhage, followed by hospitalization, medical or surgical intervention, transfusion, and change in antithrombotic therapy	Apixaban was associated with fewer gastrointestinal hemorrhages than warfarin, but this difference did not achieve statistical significance. There were also fewer soft tissue hematomas associated with apixaban that met the criteria for International Society on Thrombosis and Haemostasis (ISTH) major hemorrhage (HR, 0.46; 95% CI, 0.29 to 0.74). In addition, apixaban was associated with fewer major hemorrhages related to trauma: 37 in the apixaban group (0.24% per year) compared with 60 in the warfarin group (0.40% per year; HR, 0.60; CI, 0.40 to 0.91; P=0.015). Apixaban was associated with fewer intracranial hemorrhages than warfarin (HR, 0.42; CI, 0.30 to 0.58). Secondary: Major extracranial hemorrhage-associated adverse consequences occurred less frequently in the apixaban group than in the warfarin group, including fewer hospitalizations (HR, 0.75; CI, 0.61 to 0.92), fewer medical or surgical interventions to stop the bleeding (HR, 0.72; CI, 0.56 to 0.93), fewer transfusions (HR, 0.71; CI, 0.57 to 0.89), and fewer changes in antithrombotic therapy (HR, 0.78; CI, 0.64 to 0.95). Major ISTH hemorrhage criteria followed by death within 30 days occurred half as often in the apixaban group compared with the warfarin group (P<0.001).
Lopes et al.[33] (2019) AUGUESTUS Apixaban vs vitamin K antagonist and aspirin vs matching placebo	MC, PRO, RCT (OL for apixaban vs vitamin K antagonist; DB for aspirin vs placebo) Patients with AF who had a recent acute coronary syndrome or underwent percutaneous coronary intervention (or both) and would be using a $P2Y_{12}$ inhibitor	N=4,614 6 months	Primary: Major or clinically relevant nonmajor bleeding Secondary: Death or hospitalization and a composite of ischemic events	Primary: At six months, 10.5% of patients receiving apixaban had a major or clinically relevant nonmajor bleeding event, as compared with 14.7% receiving a vitamin K antagonist, resulting in an event rate per 100 patient-years that was lower among patients receiving apixaban than among those receiving a vitamin K antagonist (HR, 0.69; 95% CI, 0.58 to 0.81), which met the prespecified criteria for both noninferiority (P<0.001) and superiority (P<0.001). The number needed to treat over a period of six months to avoid one major or clinically relevant nonmajor bleeding event with apixaban instead of a vitamin K antagonist was 24. In the antiplatelet-regimen comparison, 16.1% of patients receiving aspirin had a major or clinically relevant nonmajor bleeding event, as compared with 9.0% receiving placebo. The event rate was higher among those receiving aspirin than among those receiving placebo (HR, 1.89; 95% CI, 1.59 to 2.24; P<0.001). The number needed to harm over a period of six months to cause one major or clinically relevant nonmajor bleeding event with aspirin instead of placebo was 14.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: At six months, 23.5% of patients who had been assigned to receive apixaban had died or had been hospitalized, as compared with 27.4% who had been assigned to receive a vitamin K antagonist. The event rate per 100 patient-years for death or hospitalization at six months was lower among patients assigned to receive apixaban than among those assigned to receive a vitamin K antagonist (HR, 0.83; 95% CI, 0.74 to 0.93; P=0.002). The difference between groups was driven by a lower incidence of hospitalization (22.5% in the apixaban group vs 26.3% in the vitamin K antagonist group) since the frequencies of death were similar. The number needed to treat over a period of six months to avoid one death or hospitalization with apixaban instead of a vitamin K antagonist was 26. In the antiplatelet-regimen comparison, 26.2% of patients who had been assigned to receive aspirin died or were hospitalized, as compared with 24.7% who had been assigned to receive placebo. Patients who had been assigned to receive aspirin had an incidence of death or hospitalization at six months that was similar to that among patients assigned to receive placebo (HR, 1.08; 95% CI, 0.96 to 1.21). At six months, 6.7% of patients who had been assigned to receive apixaban had died or had had an ischemic event — including myocardial infarction, definite or probable stent thrombosis, stroke, or urgent revascularization — as compared with 7.1% who had been assigned to receive a vitamin K antagonist. In the antiplatelet-regimen comparison, 6.5% of patients who had been assigned to receive aspirin died or had an ischemic event, as compared with 7.3% who had been assigned to receive placebo. This difference was not significant, but more ischemic events occurred in the placebo group.
Connolly et al.[34] (2009) RE-LY Dabigatran 110 mg BID vs	DB, MC, RCT Patients with AF documented on ECG performed at screening or within six months of enrollment and at least one of the	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE,	Primary: Both doses of dabigatran were non-inferior to warfarin (P<0.001). Stroke or systemic embolism occurred in 182 dabigatran 110 mg- (1.53% per year), 134 dabigatran 150 mg (-1.1% per year) and 199 warfarin-treated patients (1.69% per year). The 150 mg dose of dabigatran was “superior” to warfarin (RR, 0.66; 95% CI, 0.53 to 0.82; P<0.001), but the 110 mg dose was not (RR, 0.91; 95% CI, 0.74 to 1.11; P=0.34). Rates of hemorrhagic stroke were 0.38, 0.12 (RR, 0.31; 95% CI, 0.17 to 0.56;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	following: previous stroke or TIA, LVEF <40%, heart failure (NYHA Class ≥2) symptoms within six months before screening and ≥75 years of age or 65 to 74 years of age plus diabetes, hypertension or CAD		TIA, hospitalization	P<0.001) and 0.10% (RR, 0.26; 95% CI, 0.14 to 0.49; P<0.001) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of major bleeding (life-threatening, non-life-threatening and gastrointestinal) was 3.36, 2.71 (RR, 0.80; 95% CI, 0.69 to 0.93; P=0.003) and 3.11% (RR, 0.93; 95% CI, 0.81 to 1.07; P=0.31) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Rates of life-threatening bleeding, intracranial bleeding and major or minor bleeding were higher in warfarin-treated patients (1.80, 0.74 and 18.15%, respectively) compared to either dabigatran 110 (1.22, 0.23 and 14.62%, respectively) or 150 mg-treated patients (1.45, 0.30 and 16.42%, respectively) (P<0.05 for all comparisons of dabigatran and warfarin). There was a significantly higher rate of major gastrointestinal bleeding in dabigatran 150 mg-treated patients compared to warfarin-treated patients (P=0.43 for dabigatran 110 mg vs warfarin and P<0.001 for dabigatran 150 mg vs warfarin). The net clinical benefit outcome consisted of major vascular events, major bleeding and death. The rates of this combined outcome were 7.64, 7.09 (RR, 0.92; 95% CI, 0.84 to 1.02; P=0.10) and 6.91% (RR, 0.91; 95% CI, 0.82 to 1.00; P=0.04) per year in warfarin, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Secondary: Rates of death from any cause were 4.13, 3.75 (RR, 0.91; 95% CI, 0.80 to 1.03; P=0.13) and 3.64% (RR, 0.88; 95% CI, 0.77 to 1.00; P=0.051) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of MI was 0.53, 0.72 (RR, 1.35; 95% CI, 0.98 to 1.87; P=0.07) and 0.74% (RR, 1.38; 95%, 1.00 to 1.91; P=0.048) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of PE was 0.09, 0.12 (RR, 1.26; 95% CI, 0.57 to 2.78; P=0.56) and 0.15% (RR, 1.61; 95% CI, 0.76 to 3.42; P=0.21) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Data regarding the incidences of TIA were not reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The rate of hospitalization was 20.8, 19.4 (RR, 0.92; 95% CI, 0.87 to 0.97; P=0.003) and 20.2% (RR, 0.97; 95% CI, 0.92 to 1.03; P=0.34) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients.
Ezekowitz et al.[35] (2010) RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY Patients enrolled in the RE-LY trial who were naïve to and experienced with VKAs	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Primary: Approximately half of the patients were VKA-naïve (50.4%). Combined stroke and systemic embolism rates were similar in dabigatran 110 mg-treated patients for both the VKA-naïve and -experienced cohorts compared to warfarin-treated patients (RR, 0.93; 95% CI, 0.70 to 1.25; P=0.65 and RR, 0.87; 95% CI, 0.66 to 1.15; P=0.32). In dabigatran 150 mg-treated patients, both VKA-naïve (RR, 0.63; 95% CI, 0.46 to 0.87; P=0.005) and -experienced cohorts (RR, 0.66; 95% CI, 0.49 to 0.89; P=0.007) had significantly lower risk of stroke or systemic embolism compared to warfarin-treated patients. Major bleeding rates were lower in the VKA-experienced cohort in dabigatran 110 mg-treated patients compared to warfarin-treated patients (RR, 0.74; 95% CI, 0.60 to 0.90; P=0.003). The VKA-naïve cohort in dabigatran 110 mg-treated patients (RR, 0.87; 95% CI, 0.72 to 1.07; P=0.19) and the VKA-naïve (RR, 0.94; 95% CI, 0.77 to 1.15; P=0.55) and –experienced cohort (RR, 0.92; 95% CI, 0.76 to 1.12; P=0.41) in dabigatran 150 mg-treated patients were similar compared to warfarin-treated patients. Intracranial bleeding events were lower in dabigatran 110 VKA-naïve and -experienced cohorts (RR, 0.27; 95% CI, 0.14 to 0.52; P<0.001; RR, 0.32; 95% CI, 0.18 to 0.56; P<0.001) and in dabigatran 150 mg VKA-naïve and -experienced cohorts (RR, 0.46; 95% CI, 0.27 to 0.78; P=0.005; RR, 0.40; 95% CI, 0.24 to 0.67; P<0.001) compared to warfarin-treated patients. Secondary: Rates of life threatening bleeding, disabling stroke and death (when combined) were significantly lower in the VKA-experienced patients in both dabigatran 110 mg- (RR, 0.82; 95% CI, 0.70 to 0.96; P=0.01) and 150 mg-treated cohort (RR, 0.80; 95% CI, 0.68 to 0.93; P=0.004) compared to warfarin-treated patients, but similar for the VKA-naïve cohort. When comparing this combined outcome in VKA-naïve and -experienced cohorts within treatments, the rate was lower in VKA-experienced cohort than in the -naïve cohort (RR, 0.83; 95% CI, 0.71 to 0.98; P=0.03), as was the cardiovascular death rate (RR, 0.73; 95% CI, 0.58 to 0.92; P=0.007). In dabigatran 150 mg-treated patients, the rate of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				this combined outcome trended lower in VKA-experienced cohort. There were no differences in the rates of MI among the treatments. Gastrointestinal bleeding rates were similar for dabigatran 110 mg- and warfarin-treated patients, but significantly higher in both dabigatran 150 mg VKA-naïve (RR, 1.56; 95% CI, 1.15 to 2.10; P=0.004) and -experienced cohorts (RR, 1.42; 95% CI, 1.06 to 1.89; P=0.02) compared to warfarin-treated patients.
Diener et al.[36] (abstract) (2010) RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY Patients enrolled in the RE-LY trial who had a previous stroke or TIA	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Primary: Within the subgroup of patients with previous stroke or TIA, 1,195, 1,233 and 1,195 patients were from the dabigatran 110 mg, dabigatran 150 mg and warfarin groups. Stroke or systemic embolism occurred in 65 warfarin-treated patients (2.78% per year) compared to 55 (2.32% per year) dabigatran 110 mg- (RR, 0.84; 95% CI, 0.58 to 1.20) and 51 (2.07% per year) dabigatran 150 mg-treated patients (RR, 0.75; 95% CI, 0.52 to 1.08). The rate of major bleeding was significantly lower in dabigatran 110 mg-treated patients (RR, 0.66; 95% CI, 0.48 to 0.90), and similar in dabigatran 150 mg-treated patients (RR, 1.01; 95% CI, 0.77 to 1.34) compared to warfarin-treated patients. Secondary: The effects of both doses of dabigatran compared to warfarin were not different between patients with previous stroke or TIA and those without for any of the outcomes from RE-LY apart from vascular death (dabigatran 110 mg vs warfarin; P=0.038).
Wallentin et al.[37] (2010) RE-LY Dabigatran 110 mg BID vs	Subanalysis of RE-LY Patients enrolled in the RE-LY trial across the three treatment groups within four groups defined by	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE,	Primary: In the total population, the rate of the primary outcome of stroke and systemic embolism was reduced from 1.71% per year in warfarin-treated patients, to 1.54% per year in dabigatran 110 mg-treated patients (non inferiority; P<0.001) and to 11.1% per year in dabigatran 150 mg-treated patients ("superiority"; P<0.001). Event rates seemed to decrease with higher cTTR in warfarin-treated patients; however, there were no significant interactions between cTTR and stroke and systemic embolism in dabigatran- vs warfarin-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL) The cTTR was estimated by averaging the TTR for individual warfarin-treated patients.	quartiles of cTTR (<57.1, 57.1 to 65.5, 65.5 to 72.6 and >72.6%)		TIA, hospitalization	The rate of nonhemorrhagic stroke and systemic embolism seemed to be lower with higher cTTR in warfarin-treated patients (P=0.08). In the total population, the rate of major bleeding was 3.57% per year in warfarin-treated patients compared to 2.87 ("superiority"; P=0.003) and 3.32% ("superiority"; P=0.31) per year in dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of major bleeding, as well as major gastrointestinal bleeding, was numerically lower at higher cTTR quartiles in warfarin-treated patients. When comparing major bleedings between dabigatran 150 mg- and warfarin-treated patients, there were benefits at lower cTTR but similar results at higher cTTR (P=0.03). The rates of intracranial bleeding in warfarin-treated patients were associated with the cTTR and were consistently lower in dabigatran-treated patients than warfarin-treated patients irrespective of cTTR. There was a higher rate of major gastrointestinal bleeding in dabigatran 150 mg-treated patients compared to warfarin-treated patients at higher cTTR (P=0.019). There was an increase in total bleeding rate with increasing cTTR with all three treatments, without any significant interactions between them. Secondary: Mortality rates were 4.13, 3.75 ("superiority"; P<0.13) and 3.64% ("superiority"; P<0.051) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Total mortality was lower at higher cTTR in warfarin-treated patients; the interaction P value was 0.052 for the interaction between cTTR and the effects of dabigatran 110 mg and 0.066 for the effects of dabigatran 150 mg, with differences in mortality at lower cTTR but similar rates at higher cTTR. For all cardiovascular events, including total mortality and major bleeding, there were significantly lower event rates at higher cTTR in warfarin-treated patients. There was a significant interaction between cTTR and the composite of all cardiovascular events when comparing dabigatran 150 mg- and warfarin-treated patients (P=0.0006), and dabigatran 110 mg- and warfarin-treated patients (P=0.036). These interactions were mainly attributable to significant differences between treatments in the rates of nonhemorrhagic events (P=0.017 for dabigatran 110 mg vs warfarin and P=0.0046 for dabigatran 150 mg vs warfarin), with advantages at lower cTTR, whereas rates were greater at higher cTTR.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hohnloser et al.[38] (2012) RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY Patients with AF documented on ECG performed at screening or within six months of enrolment and at least one of the following: previous stroke or TIA, LVEF<40%, heart failure (NYHA Class ≥2) symptoms within six months before screening and ≥75 years of age or 65 to 74 years of age plus diabetes, hypertension or CAD	N=18,113 2 years	Primary: Myocardial and ischemic events Secondary: Not reported	Primary: The annual rates of MI with dabigatran 110 and 150 mg were 0.82 (HR, 1.29; 95% CI, 0.96 to 1.75; P=0.09) and 0.81% per year (HR, 1.27; 95% CI, 0.94 to 1.71; P=0.12) compared to 0.64% per year with warfarin. When both doses of dabigatran were compared to warfarin results were similar to those obtained when the two doses were compared separately. With regards to the composite outcome of MI, unstable angina, cardiac arrest, and cardiac death, annual rates were 3.16 (HR, 0.93; 95% CI, 0.80 to 1.06; P=0.28) and 33.3% per year (HR, 0.98; 95% CI, 0.85 to 1.12; P=0.77) with dabigatran 110 and 150 mg compared to 3.41% per year with warfarin. When revascularization events were included, again no significant differences emerged among the three treatments. With regards to the composite outcome of MI, unstable angina, cardiac arrest, cardiac death, revascularization events, and stroke and systemic embolic events, annual rates were 4.76 (HR, 0.93; 95% CI, 0.83 to 1.05; P=0.24) and 4.47% per year (HR, 0.88; 95% CI, 0.78 to 0.98; P=0.03) with dabigatran 110 and 150 mg compared to 5.10% per year with warfarin. Events prespecified in the net clinical benefit analysis occurred at annual rates of 7.34 (HR, 0.92; 95% CI, 0.84 to 1.01; P=0.09) and 7.11% per year (HR, 0.90; 95% CI, 0.82 to 0.99; P=0.02) with dabigatran 110 and 150 mg compared to 7.91% per year with warfarin. Patients who had at least one myocardial ischemic event were older and had more coronary risk factors compared to the remainder of the population. Across all treatments, these patients received more antiplatelet medications, β-blockers, and statins at baseline, and they also more often had a $CHADS_2$ score >2. Fifty-six of 87 clinical MIs with dabigatran 110 mg, 59/89 with dabigatran 150 mg, and 46/66 with warfarin occurred on the study drug treatment. MIs that occurred greater than six days after study drug discontinuation were observed in 17, 20, and 12 patients in all three treatment groups. Accordingly, 33, 34, and 30% of all clinical MIs were diagnosed when patients were not taking the study drug in the respective treatment arms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were 1,886 (31%) CAD/MI patients receiving dabigatran 110 mg, 1,915 (31%) receiving dabigatran 150 mg, and 1,849 (31%) receiving warfarin. The effects of dabigatran compared to warfarin were highly consistent between patients with prior CAD/MI compared to those without. Secondary: Not reported
Hart et al.[39] (2012) RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY Patients enrolled in the RE-LY trial who experienced an intracranial hemorrhage while on treatment	N=18,113 2 years	Primary: Intracranial hemorrhages occurring during anticoagulation, including sites, rates, risk factors, associated trauma and outcomes Secondary: Not reported	Primary: There were 154 intracranial hemorrhages, with an overall 30-day mortality of 36%. Intracranial hemorrhages included intracerebral hemorrhages (46%, with 49% mortality), subdural hematomas (45%, with 24% mortality) and subarachnoid hemorrhages (8%, with 31% mortality). Patients with an intracranial hemorrhage were older (P<0.001), had a history of stroke or TIA (P=0.001), more often took aspirin during follow-up (P=0.001), had lower incidence of heart failure (P=0.02) lower estimated creatinine clearances (P<0.001) compared to patients without intracranial hemorrhage. The rate of intracranial hemorrhage was higher with warfarin treatment (0.76% per year) compared to patients receiving dabigatran 150 mg (0.31% per year, RR, 0.40; 95% CI, 0.27 to 0.59) and dabigatran 110 mg (0.23% per year, RR, 0.30; 95% CI, 0.19 to 0.45). Intracranial hemorrhage-related mortality was similar between the treatments. Age was predictive of intracranial hemorrhage among patients treated with dabigatran (RR, 1.06 per year; P=0.002). The independent predictors of developing spontaneous intracerebral bleeding were the assignment to warfarin (RR, 4.1; P<0.001), previous stroke or TIA (RR, 2.7; P<0.001), aspirin use (RR, 1.8; P=0.02) and age (1.04 per year; P=0.02). The rate of spontaneous intracerebral hemorrhage was significantly higher among those assigned to warfarin (0.36% per year) compared to 0.09% per year with dabigatran 150 mg (RR, 0.26; 95% CI, 0.13 to 0.50) and 0.08% with dabigatran 110 mg (RR, 0.23; 95% CI, 0.12 to 0.47). There was no significant difference in mortality associated with spontaneous intracerebral hemorrhage between treatments. Patients with spontaneous intracerebral bleeding in the basal ganglia/thalamus were, on average, younger (P=0.04) and more likely to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				have diabetes (P=0.02) compared to those with lobar bleeding. The rate of subdural hematoma was 0.31% per year in the warfarin group compared to 0.20% per year in the dabigatran 150 mg group (RR, 0.65; P=0.10) and 0.08% per year in the dabigatran 110 mg group (RR, 0.27; P<0.001). The rate of subdural hematomas was significantly higher with dabigatran 150 mg compared to the 110 mg dosage (RR, 2.4; P=0.02). Fatal subdural bleeding occurred in 10 patients receiving warfarin compared to five and two patients receiving dabigatran 150 mg and 110 mg, respectively (P<0.05 the 110 mg group). Secondary: Not reported
Healey et al.[40] (2012) RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY Patients enrolled in the RE-LY trial who required surgery, dental procedures, cardiac catheterization, or invasive diagnostic procedures (including percutaneous biopsy, peripheral angiography, and similar procedures)	N=4,591 2 years	Primary: Perioperative major bleeding, fatal bleeding, bleeding requiring surgery and thrombotic events Secondary: Not reported	Primary: The incidence of perioperative major bleeding was not significantly different between patients receiving dabigatran 110 mg (3.8%) or dabigatran 150 mg (5.1%) compared to patients receiving warfarin (4.6%; P>0.05 for both). Perioperative fatal bleeding was similar in the dabigatran 110 mg (RR, 1.57; 95% CI, 0.26 to 9.39; P=0.62) or 150 mg treatment groups (RR, 1.01; 95% CI, 0.14 to 7.15; P=0.99) compared to the warfarin group. Bleeding requiring surgery was not significantly different in the dabigatran 110 mg (RR, 0.59; 95% CI, 0.26 to 1.33; P=0.20) or 150 mg treatment groups (RR, 1.39; 95% CI, 0.73 to 2.63; P=0.32) compared to the warfarin group. The incidences cardiovascular death, stroke (all-cause), ischemic stroke, hemorrhagic stroke, systemic embolism, MI, or PE, were low and not significantly different between patients receiving dabigatran 110 mg, 150 mg or warfarin (P>0.05 for all). Secondary: Not reported
Connolly et al.[41] (2013) RELY-ABLE	Subanalysis of RE-LY Patients enrolled in	N=5,891 28 months	Primary: Stroke (ischemic or hemorrhagic), systemic	Primary: During RELY-ABLE, the annual rates of stroke or systemic embolism were 1.46% and 1.60% per year on dabigatran 150 and 110 mg, respectively (HR, 0.91; 95% CI, 0.69 to 1.20). Annual rates of ischemic stroke (including stroke

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dabigatran 110 mg BID vs dabigatran 150 mg BID	the RE-LY trial who received dabigatran who were not discontinued medication at the time of the final RE-LY study visit and have AF and at least one risk factor for stroke		embolism, Secondary: Myocardial infarction, PE, vascular death, and total mortality	of uncertain cause) were 1.15% and 1.24% per year on dabigatran 150 and 110 mg, respectively (HR, 0.92; 95% CI, 0.67 to 1.27). Annual rates of hemorrhagic stroke were similar in the two treatment arms and were very low at 0.13% and 0.14% per year on dabigatran 150 and 110 mg, respectively. Secondary: Annual rates of myocardial infarction were also low and similar between the two groups at 0.69% and 0.72% per year. PE occurred in 0.13% and 0.11% per year on dabigatran 150 and 110 mg, respectively (HR, 1.14; 95% CI, 0.41 to 3.15). Vascular death and total mortality were not reported.
Ezekowitz et al.[42] (2007) Dabigatran 50, 150, and 300 mg BID vs warfarin, dose adjusted to maintain an INR of 2.0 to 3.0 (OL) The three doses of dabigatran were combined in a 3x3 factorial fashion with no aspirin or 81 to 325 mg of aspirin QD.	AC, DB, MC, RCT Patients with documented AF with CAD and at least one of the following: hypertension requiring medical treatment, diabetes, symptomatic heart failure (LVEF <40%), previous stroke or TIA or age >75	N=502 12 weeks	Primary: Incidence of bleeding Secondary: Suppression of D-dimer	Primary: Major bleeding events were limited to dabigatran 300 mg plus aspirin-treated patients (four patients out of 64); being statistically different compared to dabigatran 300 mg with no aspirin-treated patients (zero patients out of 150; P<0.02). There was a significant difference in major plus clinically relevant bleeding episodes (11 out of 64 vs six out of 105; P=0.03) and total bleeding episodes (25 out of 64 vs 14 out of 105; P=0.0003) between dabigatran 300 mg plus aspirin- and dabigatran 300 mg with no aspirin-treated patients. The frequency of bleeding in both dabigatran 50 mg treatment groups was significantly lower than that within the warfarin treatment group (seven out of 107 vs 12 out of 70; P=0.044). When the doses of dabigatran were compared to each other, irrespective of aspirin use, there were differences in total bleeding episodes in 300 and 150 mg- vs 50 mg-treated patients (37 out of 169 and 30 out of 169 vs seven out of 107; P=0.0002 and P=0.01, respectively). Secondary: Generally, at 12 weeks, a 13% relative increase of D-dimer plasma measurements was observed in dabigatran 50 mg-treated patients (P=0.0008) and a 3% relative increase in dabigatran 150 mg-treated patients (P=0.027) was observed. No significant changes in 300 mg dabigatran- (0%; P=0.413) or warfarin-treated patients (-1%; P=0.267) were seen. Aspirin treatment had no effect on any of these analyses.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were significantly fewer traumatic intracranial hemorrhages in patients receiving either dosage of dabigatran (11 patients for both) compared to patients receiving warfarin (24 patients; (P<0.05 for both dabigatran dosages vs warfarin). Fatal traumatic intracranial hemorrhages occurred in five, three and three patients receiving warfarin, dabigatran 150 mg, and 110 mg, respectively.
Cannon et al.[43] (2017) RE-DUAL PCI Dual therapy with dabigatran etexilate (110 mg twice daily) plus either clopidogrel or ticagrelor (110 mg dual-therapy group) vs dual therapy with dabigatran etexilate (150 mg twice daily) plus either clopidogrel or ticagrelor (150 mg dual-therapy group) vs triple therapy with warfarin plus aspirin (≤100 mg daily) and either clopidogrel or	MC, OL, RCT Patients ≥ 18 years of age with nonvalvular atrial fibrillation and had successfully undergone PCI with a bare-metal or drug-eluting stent within the previous 120 hours	N=2,725 Mean follow-up of 14 months	Primary: First major or clinically relevant nonmajor bleeding event Secondary: Composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization (PCI or coronary-artery bypass grafting)	Primary: The incidence of the primary end point was 15.4% in the 110 mg dual-therapy group as compared with 26.9% in the triple-therapy group (HR, 0.52; 95% CI, 0.42 to 0.63; P<0.001 for noninferiority; P<0.001 for superiority) and 20.2% in the 150 mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group (HR, 0.72; 95% CI, 0.58 to 0.88; P<0.001 for noninferiority). Secondary: The incidence of the composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization was 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (HR, 1.04; 95% CI, 0.84 to 1.29; P=0.005 for noninferiority). The incidence was 15.2% in the 110 mg dual-therapy group as compared with 13.4% in the triple-therapy group (HR, 1.13; 95% CI, 0.90 to 1.43; P=0.30) and 11.8% in the 150 mg dual-therapy group as compared with 12.8% in the corresponding triple-therapy group (HR, 0.89; 95% CI, 0.67 to 1.19; P=0.44).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ticagrelor (triple-therapy group)				
Giugliano et al.[44] (2013) ENGAGE AF-TIMI 48 Study Edoxaban 60 mg QD† vs edoxaban 30 mg QD† vs warfarin (adjusted dose to maintain an INR between 2.0 and 3.0) †Individuals had their dose halved (60 mg halved to 30 mg or 30 mg halved to 15 mg) if CrCl ≤ 50 mL/min, body weight ≤ 60 kg, or concomitant use of a P-glycoprotein inhibitor such as verapamil or quinidine	DB, DD, NI, RCT Patients ≥ 21 years of age with non-valvular atrial fibrillation documented by means of electrical tracing within the 12 months preceding randomization, a score of 2 or higher on the $CHADS_2$ risk assessment and anticoagulation therapy planned for the duration of the trial	N=21,105 (median follow-up 2.8 years)	Primary efficacy: Occurrence of the first stroke (ischemic or hemorrhagic) or of a systemic embolic event that occurred during treatment or within three days from the last dose taken Primary safety: Major bleeding during treatment Secondary: Composite of stroke, systemic embolism or death from cardiovascular causes	Primary efficacy: The annualized rate of stroke or systemic embolism during treatment was 1.50% (232 of 2,641 patients) with warfarin as compared with 1.18% (182 of 2,669 patients) with high-dose edoxaban (HR, 0.79; 97.5% CI, 0.63 to 0.99; P<0.001) and 1.61% (253 of 2,730 patients) with low-dose edoxaban (HR, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005). Primary safety: The annualized rate of major bleeding was 3.43% with warfarin compared with 2.75% with high-dose edoxaban (HR, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban (HR, 0.47; 95% CI, 0.41 to 0.55; P<0.001). The annualized rate of major gastrointestinal bleeding was higher with high-dose edoxaban, 1.51% compared with warfarin, 1.23% (HR, 1.23; 95% CI, 1.02 to 1.50; P=0.03). The rate was lowest with low-dose edoxaban at 0.82% (HR, 0.67; 95% CI, 0.53 to 0.83; P<0.001). Secondary: The key secondary end point of composite of stroke, systemic embolism or death from cardiovascular causes were 4.43% with warfarin compared with 3.85% for high-dose edoxaban tosylate (HR, 0.87; 95% CI, 0.78 to 0.96; P=0.005) and 4.23% for low-dose edoxaban tosylate (HR, 0.95; 95% CI, 0.86 to 1.05; P=0.32)
O'Donoghue et al.[45]	DB, DD, NI, RCT	N=21,105	Primary efficacy:	Primary: Higher-dose edoxaban significantly reduced the risk of stroke or systemic

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2015) ENGAGE AF-TIMI 48 Study Edoxaban 60 mg QD† vs edoxaban 30 mg QD† vs warfarin (adjusted dose to maintain an INR between 2.0 and 3.0) †Individuals had their dose halved (60 mg halved to 30 mg or 30 mg halved to 15 mg) if CrCl ≤ 50 mL/min, body weight ≤ 60 kg, or concomitant use of a P-glycoprotein inhibitor such as verapamil or quinidine	Patients ≥ 21 years of age with non-valvular atrial fibrillation documented by means of electrical tracing within the 12 months preceding randomization, a score of 2 or higher on the $CHADS_2$ risk assessment and anticoagulation therapy planned for the duration of the trial; For the current analysis, subjects were divided into subgroups on the basis of whether they were VKA naïve or VKA experienced	(median follow-up 2.8 years)	Occurrence of the first stroke (ischemic or hemorrhagic) or of a systemic embolic event that occurred during treatment or within three days from the last dose taken Primary safety: Major bleeding during treatment Secondary: Composite of stroke, systemic embolism or death from cardiovascular causes	embolic event in patients who were VKA naive (HR, 0.71; 95% CI, 0.56 to 0.90) and was similar to warfarin in the VKA experienced (HR, 1.01; 95% CI, 0.82 to 1.24; P interaction=0.028). Lower-dose edoxaban was similar to warfarin for stroke or systemic embolic event prevention in patients who were VKA naive (HR, 0.92; 95% CI, 0.73 to 1.15), but was inferior to warfarin in those who were VKA experienced (HR, 1.31; 95% CI, 1.08 to 1.60; P interaction=0.019). Primary safety: Both higher-dose and lower-dose edoxaban regimens significantly reduced the risk of major bleeding regardless of prior VKA experience (P interaction=0.90 and 0.71, respectively). Secondary: There were similar directional signals towards greater reductions in cardiovascular and all-cause mortality with both doses of edoxaban as compared with warfarin in patients who were VKA naive, as compared with those who were VKA experienced; however, the differences between prior VKA use subgroups were not statistically significant and therefore consistent with the overall study results.
Eisen et al.[46] (2016) ENGAGE AF-TIMI 48 Study	DB, DD, NI, RCT Patients ≥ 21 years of age with non-valvular atrial	N=9,387 (FDA-approved cohort)	Primary efficacy: Occurrence of the first stroke (ischemic or	Primary efficacy: Stroke or systemic embolism occurred in 202 patients (1.63%/y) in the edoxaban group as compared with 253 patients (2.02%/y) in the warfarin group (HR, 0.81; 95% CI, 0.67 to 0.97; P=0.023). Patients in the edoxaban group had fewer strokes than did patients in the warfarin group (1.55%/y vs 1.88%/y; HR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Edoxaban 60 mg QD† vs edoxaban 30 mg QD† vs warfarin (adjusted dose to maintain an INR between 2.0 and 3.0) †Individuals had their dose halved (60 mg halved to 30 mg or 30 mg halved to 15 mg) if CrCl ≤ 50 mL/min, body weight ≤ 60 kg, or concomitant use of a P-glycoprotein inhibitor such as verapamil or quinidine	fibrillation documented by means of electrical tracing within the 12 months preceding randomization, a score of 2 or higher on the $CHADS_2$ risk assessment and anticoagulation therapy planned for the duration of the trial; For the current analysis, subjects included had been treated with either warfarin or edoxaban 60/30 mg and had a creatinine clearance of ≤95 mL/min	(median follow-up 2.8 years)	hemorrhagic) or of a systemic embolic event that occurred during treatment or within three days from the last dose taken Primary safety: Major bleeding during treatment Secondary: Composite of stroke, systemic embolism or death from cardiovascular causes	0.82; 95% CI, 0.68 to 1.00; P=0.046). This difference was driven primarily by a significant reduction in hemorrhagic stroke with edoxaban (HR, 0.47; 95% CI, 0.31 to 0.72; P<0.001). Ischemic stroke rates were similar between the treatment groups (1.31%/y vs 1.39%/y; HR, 0.94; 95% CI, 0.76 to 1.16; P=0.97). Primary safety: The rates of major bleeding events were 3.16%/y in the edoxaban group and 3.77%/y in the warfarin group (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.023) Secondary: Key secondary end points also were decreased significantly with edoxaban as compared with warfarin. Edoxaban reduced the rate of cardiovascular death (HR, 0.84; 95% CI, 0.73 to 0.97; P=0.015) and showed a trend for the reduction of the rate of death from any cause (HR, 0.90; 95% CI, 0.81 to 1.01; P=0.084). Edoxaban achieved statistically significant superior net clinical outcomes as compared with warfarin (relative reductions of 9 to 14%).
Geller et al.[47] (2015) ENGAGE AF-TIMI 48 Study Edoxaban 60 mg QD† vs	DB, DD, NI, RCT Patients ≥ 21 years of age with non-valvular atrial fibrillation documented by means of electrical tracing within the	N=21,105 (median follow-up 2.8 years)	Primary: Time to the first systemic embolic events Secondary: Time to the first systemic embolic events	Primary: Of 1,016 patients who met the primary end point, 67 (6.6%) experienced a systemic embolic event of which 13% were fatal. Of 73 total systemic embolic events (including recurrent events), 85% involved the extremities, and 41% required a surgical or percutaneous intervention. There were 23 (0.12%/year) systemic embolic events with warfarin versus 15 with higher dose edoxaban (0.08%/year; HR vs warfarin, 0.65; 95% CI, 0.34 to 1.24; P=0.19) and 29 with lower dose edoxaban (0.15%/year; HR vs warfarin 1.24; 95% CI, 0.72 to 2.15; P=0.43).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
edoxaban 30 mg QD† vs warfarin (adjusted dose to maintain an INR between 2.0 and 3.0) †Individuals had their dose halved (60 mg halved to 30 mg or 30 mg halved to 15 mg) if CrCl ≤ 50 mL/min, body weight ≤ 60 kg, or concomitant use of a P-glycoprotein inhibitor such as verapamil or quinidine	12 months preceding randomization, a score of 2 or higher on the $CHADS_2$ risk assessment and anticoagulation therapy planned for the duration of the trial		in MA of four trials (warfarin vs RE-LY, dabigatran; ROCKET AF, rivaroxaban; ARISTOTLE, apixaban; and ENGAGE AF-TIMI 48, edoxaban)	Secondary: In a meta-analysis of four warfarin-controlled phase three AF trials, NOACs significantly reduced the risk of systemic embolic event by 37% (relative risk 0.63; 95% CI, 0.43 to 0.91; P=0.01).
Patel et al.[48] (2011) ROCKET-AF Rivaroxaban 20 mg QD (15 mg QD in patients with a creatinine clearance 30 to 49 mL/min) vs	AC, DB, DD, MC, PRO, RCT Patients with nonvalvular AF, as documented on ECG, at moderate-to high-risk for stroke, indicated by a history of stroke, TIA, or systemic embolism or at least two of the	N=14,264 590 days (median duration of treatment; 707 days median follow-up)	Primary: Composite of stroke (ischemic or hemorrhagic) and systemic embolism Secondary: Composite of stroke, systemic embolism, or death from cardiovascular	Primary: In the PP population, stroke or systemic embolism occurred in 188 rivaroxaban-treated patients (1.7% per year) compared to 241 warfarin-treated patients (2.2% per year). Rivaroxaban was non inferior to warfarin in regard to the primary outcome (HR, 0.79; 95% CI, 0.66 to 0.96; P<0.001 for non inferiority). In the as-treated safety population, the primary outcome occurred in 189 (1.7% per year) and 243 (2.2% per year) rivaroxaban- and warfarin-treated patients (HR, 0.79; 95% CI, 0.65 to 0.95; P=0.01 for superiority). In the ITT population, the primary end point occurred in 269 rivaroxaban-treated patients (2.1% per year) compared to 306 patients in warfarin-treated patients (2.4% per year; HR, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for non

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
warfarin (INR of 2.0 to 3.0)	following risk factors: heart failure or LVEF ≤35%, hypertension, age ≥75 years, or diabetes mellitus The proportion of patients who had not had a previous ischemic stroke, TIA, or systemic embolism and who had less than two risk factors was limited to 10% of the cohort for each region; the remainder of patients were required to have had either previous thromboembolism or at least three risk factors		causes; composite of stroke, systemic embolism, death from cardiovascular causes, or MI; individual components of composite outcomes; major and nonmajor clinically relevant bleeding events	inferiority; P=0.12 for superiority). Secondary: In the on-treatment population, the composite of stroke, systemic embolism, or vascular death occurred in significantly fewer rivaroxaban-treated patients compared to warfarin treated patients (3.11 vs 5.79% per year, respectively; HR, 0.86; 95% CI 0.74 to 0.99; P=0.034). In the on-treatment population, the composite of stroke, systemic embolism, vascular death or MI occurred in significantly fewer rivaroxaban-treated patients compared to warfarin treated patients (3.91 vs 4.62% per year, respectively; HR, 0.85; 95% CI 0.74 to 0.96; P=0.010). In the on-treatment population, stroke occurred in 184 (2.61%) and 221 (3.12%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (1.65 vs 1.96% per year; HR, 0.85; 95% CI, 0.70 to 1.03; P=0.092). In the on-treatment population, non-central nervous system systemic embolism occurred in five (0.07%) and 22 (0.31%) rivaroxaban- and warfarin-treated patients; the event rate was significantly lower with rivaroxaban (0.04 vs 0.19% per year; HR, 0.23; 95% CI, 0.09 to 0.61; P=0.003). In the on-treatment population, vascular death occurred in 170 (2.41%) and 193 (2.73%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (1.53 vs 1.71% per year; HR, 0.89; 95% CI, 0.73 to 1.10; P=0.289). In the on-treatment population, MI occurred in 101 (1.43%) and 126 (1.78%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (0.91 vs 1.12% per year; HR, 0.81; 95% CI, 0.63 to 1.06; P=0.121). There was no difference in major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin. Bleeding occurred in 1,475 and 1,449 rivaroxaban- and warfarin-treated patients (14.9 and 14.5% per year, respectively; HR, 1.03; 95% CI, 0.96 to 1.11; P=0.44).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The incidence of major bleeding was similar with rivaroxaban and warfarin (3.6 and 3.4%, respectively; P=0.58). Decreases in hemoglobin levels ≥2 g/dL and transfusions were more common among rivaroxaban-treated patients, whereas fatal bleeding and bleeding at critical anatomical sites were less frequent compared to warfarin treated patients. Rates of intracranial hemorrhage were significantly lower with rivaroxaban compared to warfarin (0.5 vs 0.7% per year; HR, 0.67; 95% CI, 0.47 to 0.93; P=0.02). Major bleeding from a gastrointestinal site was more common with rivaroxaban, with 224 bleeding events (3.2%), compared to 154 events (2.2%) with warfarin (P<0.001).
Hankey et al.[49] (2012) ROCKET-AF Rivaroxaban 20 mg QD (15 mg QD in patients with a creatinine clearance 30 to 49 mL/min) vs warfarin (INR of 2.0 to 3.0)	Subanalysis of ROCKET-AF[35] Patients enrolled in the ROCKET-AF trial stratified based on previous stroke and TIA	N=14,264 (previous stroke or TIA; n=7,468) 590 days (median duration of treatment; 707 days median follow-up)	Primary: Composite of stroke (ischemic or hemorrhagic) and systemic embolism Secondary: Safety, major and nonmajor clinically relevant bleeding events	Primary: The number of events per 100 person-years for the primary endpoint in patients receiving rivaroxaban compared to patients receiving warfarin was consistent among patients with previous stroke or TIA (2.79 vs 2.96%; HR, 0.94; 95% CI, 0.77 to 1.16) and those without (1.44 vs 1.88%; HR, 0.77; 95% CI, 0.58 to 1.01; P=0.23). Secondary: The overall number of adverse events per 100 person-years was similar with both treatments and in patients with and without previous stroke or TIA. The number of major and nonmajor clinically relevant bleeding events per 100 person-years in patients receiving rivaroxaban and warfarin was consistent among patients with previous stroke or TIA (13.31 vs 13.87%; HR, 0.96; 95% CI, 0.87 to 1.07) and those without (16.69 vs 15.19%; HR, 1.10; 95% CI, 0.99 to 1.21; P=0.08). The number of major bleeding events per 100 person-years among patients who received at least one dose of study drug was significantly lower among those with previous stroke or TIA (n=318, 3.18%) compared to those without (n=420, 3.89%; HR, 0.81; 95% CI, 0.70 to 0.93; P=0.0037), but the safety of rivaroxaban compared to warfarin with respect to major bleeding showed no interaction among patients with (HR, 0.97; 95% CI, 0.79 to 1.19) and without previous stroke or TIA (HR, 1.11; 95% CI, 0.92 to 1.34; P=0.36). The effect of rivaroxaban compared to warfarin on intracerebral hemorrhage

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was consistent among patients with (HR, 0.84; 95% CI, 0.50 to 1.41) and without previous stroke or TIA (HR, 0.46; 95% CI, 0.24 to 0.89; P=0.16).
Halperin et al.[50] (2014) ROCKET-AF Rivaroxaban 20 mg QD (15 mg QD in patients with a creatinine clearance 30 to 49 mL/min) vs warfarin (INR of 2.0 to 3.0)	Subanalysis of ROCKET-AF[35] Patients enrolled in the ROCKET-AF trial stratified by age ≥75 or <75 years	N=14,264 590 days (median duration of treatment; 707 days median follow-up)	Primary: Stroke (ischemic or hemorrhagic) and systemic embolism Secondary: Bleeding complications	Primary: Stroke and systemic embolism were more common in patients aged ≥75 years than in those aged <75 years (2.57 vs 2.05 per 100 patient-years; P=0.0068). In older patients, the primary event rate was 2.29 (95% CI, 1.92 to 2.73) per 100 patient-years with rivaroxaban compared with 2.85 (95% CI, 2.43 to 3.34) per 100 patient-years with warfarin (HR=0.80; 95% CI, 0.63 to 1.02). In younger patients, the primary event rate was 2.00 (95% CI, 1.69 to 2.35) per 100 patient-years with rivaroxaban compared with 2.10 (95% CI, 1.79 to 2.46) per 100 patient-years with warfarin (HR=0.95; 95% CI, 0.76 to 1.19). There was no significant interaction of treatment efficacy with age for the primary end point (P=0.3131). Secondary: Rates of major bleeding were higher among older patients (4.63 [4.21 to 5.09] per 100 patient-years) than in younger patients (2.74 [2.47 to 3.04]; P<0.0001). There were no significant differences, however, in rates of major bleeding among patients on rivaroxaban compared with those on warfarin in either age group.
Jones et al.[51] (2014) ROCKET-AF Rivaroxaban 20 mg QD (15 mg QD in patients with a creatinine clearance 30 to 49 mL/min) vs warfarin (INR of 2.0 to 3.0)	Subanalysis of ROCKET-AF[35] Patients enrolled in the ROCKET-AF trial stratified by peripheral artery disease (PAD)	N=14,264 (PAD; n=839) 590 days (median duration of treatment; 707 days median follow-up)	Primary: Stroke or systemic embolism, bleeding events Secondary: All-cause death, MI, and the composite (and individual components) of stroke, systemic embolism, or vascular death	Primary: The overall rate of stroke or non-CNS systemic embolism was not statistically significantly different among patients with PAD compared with those without PAD (2.41 vs 2.09 events/100 patient-years; adjusted HR, 1.04; 95% CI, 0.72 to 1.50; P=0.84). The overall rate of major or non-major clinically relevant bleeding was also not statistically significantly different among patients with PAD compared with those without PAD (17.81 vs 14.54; HR, 1.11; CI, 0.96 to 1.28; P=0.17). Secondary: No differences in treatment effect were detected between patients with and without PAD for any of the secondary efficacy endpoints.
Anderson et al.[52]	MA (15 RCTs)	N=16,058	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Warfarin (INR ≥2.0) vs placebo, antiplatelet agents (aspirin, aspirin plus clopidogrel, indobufen*), low dose warfarin and low dose warfarin plus aspirin Results for aspirin plus clopidogrel and indobufen were not reported.	Patients ≥18 years of age with AF or atrial flutter	≥3 months	Incidence of systemic embolism and major bleeding Secondary: Not reported	Warfarin vs placebo Four trials compared the efficacy of warfarin vs placebo for prevention of thromboembolic events (n=1,909). Eleven systemic embolic events were observed; two and nine in warfarin- and placebo-treated patients (OR, 0.29; 95% CI, 0.08 to 1.07; P=0.06). The rates of major bleeding were higher in warfarin-treated patients in three trials. The combined OR for major bleeding was higher in warfarin-treated patients (OR, 3.01; 95% CI, 1.31 to 6.92; P=0.01). Warfarin vs antiplatelet agents Nine trials compared the efficacy of warfarin and antiplatelet agents for the prevention of systemic embolism (n=11,756). Thirty-four and 71 systemic embolism events occurred in warfarin- and antiplatelet-treated patients (OR, 0.50; 95% CI, 0.33 to 0.75; P<0.001). Pooled analysis for the risk of major bleeding showed no evidence of increased risk with warfarin treatment (OR, 1.07; 95% CI, 0.85 to 1.34; P=0.59). Warfarin vs low dose warfarin or a combination of low dose warfarin and aspirin Five trials compared warfarin vs low dose warfarin or the combination of low dose warfarin and aspirin for the prevention of thromboembolic events. Four trials compared warfarin directly with low dose warfarin (n=1,008), and five and three patients had an embolic event (OR, 1.52; 95% CI, 0.40 to 5.81; P=0.54). Two trials compared warfarin to low dose warfarin and aspirin (n=1,385); two patients in each group had a systemic embolic event (OR, 1.00; 95% CI, 0.17 to 5.81; P=1.00). The risk of major bleeding was higher in warfarin-treated patients compared to low dose warfarin-treated patients (OR, 2.88; 95% CI, 1.09 to 7.60; P=0.03), but there was no difference when comparing warfarin-treated patients to low dose warfarin and aspirin-treated patients (OR, 1.14; 95% CI, 0.55 to 2.36; P=0.72). All trials were stopped early owing to the "superiority" of warfarin treatment in stroke prevention seen in other trials. Secondary: Not reported
Agarwal et al.[53] (2012)	MA (8 RCTs)	N=32,053 (55,789	Primary: Ischemic or	Primary: The rate of stroke or non-central nervous system embolism varied from 1.2 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Warfarin vs alternative thromboprophylaxis (ximelagatran*, idraparinux*, aspirin, aspirin plus clopidogrel, dabigatran, rivaroxaban, apixaban)	Patients with nonvalvular AF	patient-years) Duration not specified	hemorrhagic stroke or non-central nervous system embolism Secondary: MI, all-cause mortality, composite adverse vascular events (stroke, non-central nervous system embolism, MI, and death), major bleeding, intracranial hemorrhage, clinically relevant nonmajor bleeding, minor bleeding	2.3% per year. The pooled event rate for stroke or non-central nervous system embolism was calculated to be 1.66% (95% CI, 1.41 to 1.91) per year. There was a significantly higher incidence of stroke and non-central nervous system embolism in patients ≥75 years (2.27% per year) compared to those <75 years of age (1.62% per year; P<0.001). A significantly higher pooled incidence of stroke or non-central nervous system embolism in females compared to males (P<0.01) and in patients with a history of stroke or TIA compared to patients without previous events (P=0.001). Patients with no history of exposure to VKA had a significantly higher incidence of stroke and non-central nervous system embolism compared to patients who reported use of VKA at the time of enrollment (RR, 1.16; 95% CI, 1.01 to 1.33). Pooled analysis stratified by $CHADS_2$ score yielded pooled annual event rates of 0.89% (95% CI, 0.66 to 1.13) per year for scores ≤1, 1.43% (95% CI, 1.19 to 1.66) per year for scores of 2, and 2.50% (95% CI, 2.17 to 2.82) per year for scores ≥3. Compared to with the lowest risk $CHADS_2$ category, the RR of stroke or non-central nervous system embolism was significantly higher with intermediate risk category (RR, 1.46; 95% CI, 1.13 to 1.89; P=0.004) and in the high risk category (RR, 2.89; 95% CI, 2.28 to 3.66; P<0.001). Secondary: Rates of MI, all-cause mortality, and composite vascular events varied from 0.53 to 1.40% per year, 2.21 to 8.00% per year, and 3.93 to 5.90% per year, respectively. Pooled event rates for MI, all-cause mortality, and composite vascular events were calculated to be 0.76% (95% CI, 0.57 to 0.96) per year, 3.83% (95% CI, 3.07 to 4.58) per year, and 4.80% (95% CI, 4.22 to 5.38) per year, respectively. The incidence of major bleeding episodes ranged from 1.40 to 3.40% per year. The annual rate of intracranial hemorrhage in patients with AF taking warfarin ranged from 0.33 to 0.80% per year. MA of intracranial hemorrhage yielded a pooled event rate of 0.61% (95% CI, 0.48 to 0.73) per year. The cumulative adverse event rate, defined as major vascular events reported or death or major bleedings episodes, was observed to range from 3.00% per year in one trial to 7.64% per year in another.
Saxena et al.[54] (2004)	SR (2 RCTs) Patients with	N=485 1.7 to 2.3	Primary: Fatal or non-fatal recurrent stroke,	Primary: In one RCT, the annual rate of all vascular events was eight vs 17% in oral anticoagulation and placebo-treated patients. The risk of stroke was reduced

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Oral anticoagulants (warfarin) vs placebo Target INR ranges in patients receiving oral anticoagulants were 2.5 to 4.0 and 1.4 to 2.8 in the two RCTs included in the review.	nonrheumatic AF and a previous TIA or minor ischemic stroke	years	all major vascular events (vascular death, recurrent stroke, MI, and systemic embolism), any intracranial bleed, major extracranial bleed Secondary: Not reported	from 12 to four percent per year. In absolute terms, 90 vascular events (mainly strokes) were prevented per 1,000 patients treated with oral anticoagulation per year. There were eleven out of 225 nonvascular deaths in oral anticoagulation-treated patients compared to nine out of 214 nonvascular deaths in placebo-treated patients, and 30 out of 225 and 35 out of 214 vascular deaths. In the same trial, the incidence of all bleeding events while receiving oral anticoagulation was low (2.8 vs 0.7% per year). The absolute annual excess of major bleeds was 21 per 1,000 patients treated, with no documented intracerebral bleeding. In the second RCT, four and two placebo- and oral anticoagulation-treated patients had a recurrent stroke. The number of all vascular events was eight out of 21 in warfarin-treated patients compared to eleven out of 25 in placebo-treated patients (OR, 0.78; 95% CI, 0.20 to 2.9). In the same trial, no intracranial bleeds occurred. Combined results demonstrate that oral anticoagulation is highly effective; it reduces the odds of recurrent stroke (disabling and non-disabling) by two-thirds (OR, 0.36; 95% CI, 0.22 to 0.58) and it almost halves the odds of all vascular events (OR, 0.55; 95% CI, 0.37 to 0.82). The benefit is not negated by an unacceptable increase of major bleeding complications (OR, 4.32; 95% CI, 1.55 to 12.10). In both trials, no intracranial bleeds were reported in oral anticoagulation-treated patients (OR, 0.13; 95% CI, 0.00 to 6.49). Secondary: Not reported
Aguilar et al.[55] (2005) Oral anticoagulants (warfarin [and congeners*] and orally active DTIs) vs control or placebo	SR (5 RCTs) Patients with AF without prior stroke or TIA	N=2,313 1.5 years (mean follow-up; range, 1.2 to 2.3 years)	Primary: All strokes Secondary: Ischemic strokes, all disabling or fatal stroke, MI, systemic emboli, all intracranial hemorrhage, major	Primary: Consistent reductions were likewise evident in all trials, with an overall OR of 0.39 (95% CI, 0.26 to 0.59). About 25 strokes would be prevented yearly per 1,000 patients given oral anticoagulants. Secondary: Warfarin was associated with a reduction in ischemic stroke in all five trials, which was significant in four (pooled analysis vs control: OR, 0.34; 95% CI, 0.23 to 0.52). With the annualized rate of ischemic stroke in the control group of about four percent per year, the absolute reduction by oral anticoagulants was about 2.6% per year for patients without prior stroke or TIA, or about 25

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			extracranial hemorrhage, vascular death, composite of all stroke, MI or vascular death, all-cause mortality	ischemic strokes saved yearly per 1,000 patients given warfarin. Consistent reductions in all disabling or fatal strokes were seen in all trials, not reaching statistical significance in individual trials but with a significant reduction in pooled analysis (OR, 0.47; 95% CI, 0.28 to 0.80). About 12 of these serious strokes would be prevented yearly for every 1,000 participants given warfarin. Fifteen MIs occurred in three trials; therefore, no meaningful estimate of the effect of oral anticoagulants on this outcome could be made (OR, 0.87; 95% CI, 0.32 to 2.42). Ten systemic emboli occurred in the five trials; therefore, no meaningful estimate of the effect of oral anticoagulants could be made, but with the trend similar to that for ischemic stroke (OR, 0.45; 95% CI, 0.13 to 1.57). Seven intracranial hemorrhages occurred, with a nonsignificant trend toward the expected increase (OR, 2.38; 95% CI, 0.54 to 10.50). Major extracranial hemorrhage was similar in warfarin-treated patients, but with wide CIs due to the relatively small number of events (OR, 1.07; 95% CI, 0.53 to 2.12). A nonsignificant trend favoring treatment with warfarin was seen (OR, 0.84; 95% CI, 0.56 to 1.30) for vascular death. For the composite of stroke, MI or vascular death, the OR with oral anticoagulants was 0.57 (95% CI, 0.42 to 0.76). About 25 of these events would be prevented per year for every 1,000 patients given warfarin. Sixty-nine and 99 deaths occurred in warfarin- and control-treated patients (OR, 0.69; 95% CI, 0.50 to 0.94). The mortality rate averaged 5% per year in the control group. About 17 deaths would be prevented per year for every 1,000 AF patients given warfarin.
Ruff et al.[56] (2014)	MA (4 trials; RE-LY, ROCKET-AF, ARISTOTLE, and	N=71,683 Median	Primary: Stroke and systemic	Primary: Allocation to a new oral anticoagulant significantly reduced the composite of stroke or systemic embolic events by 19% compared with warfarin. The benefit

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
New oral anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban) vs warfarin	ENGAGE AF-TIMI) Patients with AF	follow-up ranged from 1.8 to 2.8 years	embolic events, ischemic stroke, hemorrhagic stroke, all-cause mortality, MI, major bleeding, intracranial hemorrhage, and gastrointestinal bleeding Secondary: Not reported	was mainly driven by a large reduction in hemorrhagic stroke. New oral anticoagulants were also associated with a significant reduction in all-cause mortality. The drugs were similar to warfarin in the prevention of ischemic stroke and myocardial infarction. Randomization to a high-dose new oral anticoagulant was associated with a 14% non-significant reduction in major bleeding. In line with the reduction in hemorrhagic stroke, a substantial reduction in intracranial hemorrhage was observed, which included hemorrhagic stroke, and subdural, epidural, and subarachnoid bleeding. New oral anticoagulants were, however, associated with increased gastrointestinal bleeding. A greater relative reduction in bleeding with new oral anticoagulants was found at centers that achieved a center-based time in therapeutic range of less than 66% than at those achieving a time in therapeutic range of 66% or more. Secondary: Not reported
Ezekowitz et al.[57] (1999) Warfarin vs aspirin vs warfarin plus aspirin A total of 10 trials were included: five primary prevention PC trials, one secondary prevention trial,	MA (10 trials) Patients with AF	N=not reported 1.2 to 2.3 years (average follow-up)	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Pooled analysis from the five PC, primary prevention trials demonstrate the value of warfarin for reducing the risk of stroke was consistent among trials and decreased the risk by 68% (4.5 to 1.4% per year) with virtually no increase in the frequency of major bleeding (rates: 1.2, 1.0 and 1.0% per year for warfarin, aspirin and placebo, respectively). Two of these trials evaluated aspirin for the primary prevention of stroke. In one trial, aspirin use was associated with a 42% reduction in stroke and in the other; the reduction of stroke with aspirin compared to placebo was 36%. The primary prevention trials demonstrate that warfarin is “superior” to both aspirin and placebo, with aspirin being more effective than placebo for preventing stroke. The annual rate of the main outcome measures of death due to vascular disease, any stroke, MI or systemic embolism in the secondary prevention trial was 8%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
one trial comparing warfarin to aspirin, and three trials of warfarin plus aspirin.				per year in warfarin-treated patients and 17% per year in placebo-treated patients. Treatment with warfarin reduced the risk of stroke from 12 to 4% per year (66% reduction). Among the aspirin-treated patients, the incidence of outcome events was 15% per year compared to 19% per year among placebo-treated patients. The incidence of major bleeding was low in this trial: 2.8, 0.9 and 0.7% per year for warfarin, aspirin and placebo. In the trial comparing warfarin to aspirin for the primary prevention of stroke, the primary event rate was 1.3 and 1.9% per year in warfarin- and aspirin-treated patients (RR, 0.67; P=0.24), and by ITT analysis there was no benefit from treatment with warfarin. Of note, the trial was not adequately powered to show a difference between the two treatments. Patients >75 years of age had a substantial risk of thromboembolism during treatment with aspirin (4.8% per year); treatment with warfarin reduced the risk to 3.6% per year (RR, 0.73; P=0.39). The trial evaluating warfarin in combination with aspirin to warfarin monotherapy in AF patients with at least one prespecified risk factor for thromboembolic disease was terminated after a mean follow-up of 1.1 years because the rate of ischemic stroke and systemic embolization in combination-treated patients was 7.9% per year compared to 1.9% per year in warfarin-treated patients (P<0.001). The rates of major bleeding were similar in both treatments.
Reduce the Risk of Major Cardiovascular Events in Patients with Chronic Coronary Artery Disease or Peripheral Artery Disease				
Eikelboom et al.[58] (2017) COMPASS Rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) vs rivaroxaban (5 mg twice daily) with an	DB, RCT Patients meeting the criteria for coronary artery disease, peripheral arterial disease, or both	N=27,395 Variable duration	Primary: Composite of cardiovascular death, stroke, or myocardial infarction Primary Safety: Major bleeding Secondary: Composite of ischemic stroke,	Primary: A primary outcome event occurred in 4.1% of patients who were assigned to rivaroxaban plus aspirin, 4.9% who were assigned to rivaroxaban alone, and 5.4% who were assigned to aspirin alone. For the comparison of rivaroxaban (2.5 mg twice daily) plus aspirin with aspirin alone, the HR for the primary outcome was 0.76 (95% CI, 0.66 to 0.86; P<0.001). For the comparison of rivaroxaban (5 mg twice daily) alone with aspirin alone, the HR was 0.90 (95% CI, 0.79 to 1.03; P=0.12). Primary Safety: Major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (3.1% vs 1.9%; HR, 1.70; 95% CI, 1.40 to 2.05; P<0.001). Major bleeding events occurred in more patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin-matched placebo once daily vs aspirin (100 mg once daily) with a rivaroxaban-matched placebo twice daily			myocardial infarction, acute limb ischemia, or death from coronary heart disease; the composite of ischemic stroke, myocardial infarction, acute limb ischemia, or cardiovascular death; and death from any cause	rivaroxaban-alone group than in the aspirin-alone group (2.8% vs 1.9%; HR, 1.51; 95% CI, 1.25 to 1.84; P<0.001). Secondary: The secondary composite outcome of ischemic stroke, myocardial infarction, acute limb ischemia, or death from coronary heart disease occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (3.6% vs 4.9%; HR, 0.72; 95% CI, 0.63 to 0.83; P<0.001). The secondary outcome of ischemic stroke, myocardial infarction, acute limb ischemia, or cardiovascular death also occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (4.3% vs 5.7%; HR, 0.74; 95% CI, 0.65 to 0.85; P<0.001). There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (HR, 0.82; 95% CI, 0.71 to 0.96; P=0.01). The threshold P value using the Hochberg procedure for each of the above comparisons was 0.0025. For the regimen of rivaroxaban alone as compared with aspirin alone, because no significant effect was seen for the primary composite outcome, formal testing of the secondary outcomes was not performed.
Eikelboom et al.[59] (2021) COMPASS Rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) vs aspirin (100 mg once daily) with a rivaroxaban-matched placebo twice daily	DB, RCT Patients meeting the criteria for coronary artery disease, peripheral arterial disease, or both	N=18,278 Variable duration (median of 23 months)	Primary: Mortality Secondary: Not reported	Primary: The combination of rivaroxaban and aspirin compared with aspirin alone reduced mortality by 18% (3.4% vs 4.1%; HR, 0.82; 95% CI, 0.71 to 0.96; P=0.01). The combination also significantly reduced cardiovascular mortality (1.7% vs 2.2%; HR, 0.78; 95% CI, 0.64 to 0.96; P=0.02) but not non-cardiovascular death (1.7% vs 1.9%; HR, 0.87; 95% CI, 0.70 to 1.08; P=0.20). Among causes of cardiovascular death, the combination compared with aspirin alone was associated with a consistent pattern of reduced mortality except for deaths after heart failure. Secondary: Not reported
Bonaca et al.[60] (2020)	DB, MC, RCT Patients ≥50 years	N=6,564 Median	Primary: Composite of acute limb	Primary: The primary composite outcome occurred in 508 patients in the rivaroxaban group and in 584 patients in the placebo group; the Kaplan–Meier estimates of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) vs aspirin (100 mg once daily) with a rivaroxaban-matched placebo twice daily	of age with had documented lower-extremity peripheral artery disease, including symptoms, anatomical evidence, and hemodynamic evidence; patients were eligible after a successful revascularization procedure performed within the previous 10 days for symptoms of peripheral artery disease	follow-up of 28 months	ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes Secondary: Bleeding	the incidence at three years were 17.3% and 19.9%, respectively (HR, 0.85; 95% CI, 0.76 to 0.96; P=0.009). Secondary: The principal safety outcome of TIMI major bleeding during follow-up occurred in 62 patients in the rivaroxaban group and 44 patients in the placebo group, with Kaplan–Meier estimates of the incidence at three years of 2.65% and 1.87%, respectively (HR, 1.43; 95% CI, 0.97 to 2.10; P=0.07).
Zannad et al.[61] (2018) COMMANDER HF Rivaroxaban 2.5 mg twice daily vs placebo Treatment in addition to standard care after treatment for an episode of worsening heart failure	DB, MC, RCT Patients who had chronic heart failure, a LVEF ≤40%, coronary artery disease, and elevated plasma concentrations of natriuretic peptides and who did not have atrial fibrillation	N=5,022 Median follow-up of 21.1 months	Primary: Composite of death from any cause, MI, or stroke Secondary: Bleeding	Primary: The primary efficacy outcome occurred in 25.0% of patients assigned to rivaroxaban and 26.2% of patients assigned to placebo (HR, 0.94; 95% CI, 0.84 to 1.05; P=0.27). Secondary: The principal safety outcome of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability occurred in 18 patients (0.7%) assigned to rivaroxaban and 23 (0.9%) assigned to placebo (HR, 0.80; 95% CI, 0.43 to 1.49; P=0.48). Fatal bleeding events occurred in nine patients in each group, but fewer critical-space bleeding events occurred in the rivaroxaban group than in the placebo group (13 [0.5%] vs. 20 [0.8%]; HR, 0.67; 95% CI, 0.33 to 1.34; P=0.25).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Reduce the Risk of Death, Recurrent MI, and Thromboembolic Events Such as Stroke or Systemic Embolization After MI				
Rothberg et al.[62] (2005) Warfarin (high intensity) plus aspirin vs aspirin	MA (10 RCTs) Patients with ACS who were not stented	N=5,938 3 months to 4 years (follow-up)	Primary: MI, stroke, revascularization Secondary: Not reported	Primary: The annualized rate of MI in aspirin-treated patients ranged from 0.03 to 0.93. Nine of the ten trials found a risk reduction attributable to treatment with warfarin, but only two trials were sufficiently powered for the reduction to reach statistical significance. Reductions in RR ranged from 29 to 100%, with an overall RR of 44%. The annualized risk for ischemic stroke in aspirin-treated patients ranged from 0.000 to 0.080, with a weighted average of 0.008. In the five trials in which at least one stroke was reported, a risk reduction for warfarin plus aspirin-treated patients was found, but only one risk reduction was statistically significant. Reductions in the RR ranged from 50 to 100%, with an overall RR of 54% (CI, 23 to 73). Overall, four hemorrhagic strokes occurred in warfarin-treated patients and one in aspirin-treated patients, translating to one additional intracranial hemorrhage per 1,800 patient-years of combined anticoagulation. The annualized risk for revascularization ranged from 0.076 to 1.300. Five of the seven trials showed decreased rates of percutaneous transluminal coronary angioplasty or CABG for warfarin-treated patients, but only one rate reached statistical significance. HRs ranged from 0.51 to 1.70, with an overall RR reduction of 20% (95% CI, 5 to 33). No trial showed a significant difference in mortality. The combined trials showed a four percent decrease in overall mortality in warfarin-treated patients, but this did not reach significance (P value not reported). Nine trials showed an increased risk for major bleeding associated warfarin treatment. The annualized risk for major bleeding in warfarin-treated patients ranged from 0.6 to 18.0%, with an overall risk of 1.5%. The RR for major bleeding with warfarin treatment compared to aspirin was 2.5 (95% CI, 1.7 to 3.7). The RR for minor bleeding was 2.6 (95% CI, 2.0 to 3.3). Secondary: Not reported
Prophylaxis and/or Treatment of Venous Thromboembolism				
Cohen et al.[63]	AC, DB, DD, MN,	N=7,513	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2016) APEX Betrixaban 160 mg day one followed by 80 mg QD for 35 to 42 days and enoxaparin SC placebo QD for 6 to 14 days vs enoxaparin 40 mg SC QD for 6 to 14 days and betrixaban placebo QD for 35 to 42 days (Of note, the following individuals received alternate dosing regimens: those with severe renal impairment [CrCl ≥15 mL/min and < 30 mL/min]: betrixaban 80 mg day one followed by 40 mg QD or enoxaparin 20 mg QD; those on concomitant P-gp inhibitor administration:	RCT Patients ≥40 years of age hospitalized for <96 hours for an acute medical illness (heart failure, respiratory failure, infectious disease, rheumatic disease or ischemic stroke) at risk for VTE due to moderate or severe immobility (at least 24 hours), and additional risk factors for VTE (≥75 years of age, 60 to 74 years of age with D-dimer ≥2 ULN or 40 to 59 years of age with D-dimer ≥2 ULN and a history of either VTE or cancer) (While the study was ongoing [after 35% enrollment], the study was amended to restrict further enrollment to patients ≥ 75 years of age or with D-dimer	35 to 42 days	Composite of asymptomatic proximal DVT between day 32 and day 47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE between day 1 and day 42 Secondary: Composite of symptomatic VTE through day 42 and a composite of asymptomatic proximal DVT between day 32 and day 47, symptomatic DVT, nonfatal PE or death from any cause through day 42	*Cohort 1 (patients with an elevated D-dimer level)* In the betrixaban group, 6.9% of patients had the primary efficacy outcome compared to 8.5% of the enoxaparin group (RR in betrixaban group, 0.81; 95% CI, 0.65 to 1.00; P=0.054). *Cohort 2 (patients with an elevated D-dimer level or an age of at least 75 years):* In the betrixaban group, 5.6% of patients had the primary efficacy outcome compared to 7.1% of the enoxaparin group (RR in betrixaban group, 0.80; 95% CI, 0.66 to 0.98; P=0.03). *Cohort 3 (Overall population):* In the betrixaban group, 5.3% of patients had the primary efficacy outcome compared to 7.0% of the enoxaparin group (RR in betrixaban group, 0.76; 95% CI, 0.63 to 0.92; P=0.006). *Cohort 2 and cohort 3 were exploratory* Secondary: *Cohort 1 (patients with an elevated D-dimer level)* In the betrixaban group, 1.3% of patients had a symptomatic VTE compared to 1.9% of the enoxaparin group (RR, 0.67; 95% CI, 0.42 to 1.07; P=0.09). In the betrixaban group, 11.5% of patients had the primary efficacy outcome plus death from any cause compared to 12.9% of the enoxaparin group (RR, 0.89; 95% CI, 0.75 to 1.05; P=0.16). *Cohort 2 (patients with an elevated D-dimer level or an age of at least 75 years):* In the betrixaban group, 1.0% of patients had a symptomatic VTE compared to 1.4% of the enoxaparin group (RR, 0.71; 95% CI, 0.46 to 1.09; P=0.11). In the betrixaban group, 9.8% of patients had the primary efficacy outcome plus death from any cause occurred in compared to 10.9% of the enoxaparin group (RR, 0.90; 95% CI, 0.77 to 1.04; P=0.15). *Cohort 3 (Overall population):* In the betrixaban group, 0.9% of patients had a symptomatic VTE compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
betrixaban 80 mg day one followed by 40 mg QD or enoxaparin 40 mg SC QD)	values > 2 x ULN)			1.5% of the enoxaparin group (RR, 0.64; 95% CI, 0.42 to 0.98; P=0.04). In the betrixaban group, 9.2% of patients had the primary efficacy outcome plus death from any cause compared to 10.8% of the enoxaparin group (RR, 0.85; 95% CI, 0.73 to 0.98; P=0.02).
Anderson et al.[64] (2018) Patients who were undergoing total knee arthroplasty were then randomly assigned to receive an additional 9 days of either 10 mg of oral rivaroxaban or 81 mg of aspirin once daily Patients who were undergoing total hip arthroplasty were randomly assigned to receive an additional 30 days of once-daily rivaroxaban (10 mg) or aspirin (81 mg)	DB, MC, RCT Patients who were undergoing elective unilateral primary or revision hip or knee arthroplasty and received in-hospital prophylaxis with oral rivaroxaban at a dose of 10 mg once daily, starting on the day of the surgery (not less than six hours after wound closure) or on postoperative day one, depending on local practice; this regimen was followed by daily administration up to and including postoperative day five	N=3,424 90 days	Primary: Symptomatic venous thromboembolism Secondary: Bleeding, including major or clinically relevant nonmajor bleeding; death	Primary: Symptomatic proximal deep-vein thrombosis or pulmonary embolism developed in 11 of 1707 patients (0.64%) in the aspirin group and in 12 of 1717 patients (0.70%) in the rivaroxaban group (difference, 0.06 percentage points; 95% CI, –0.55 to 0.66). In the comparison with rivaroxaban, aspirin was found to be noninferior (P<0.001) but not superior (P=0.84) for the prevention of postoperative proximal deep-vein thrombosis or pulmonary embolism. Secondary: Major bleeding events occurred in eight patients (0.47%) in the aspirin group and in five patients (0.29%) in the rivaroxaban group (difference, 0.18 percentage points; 95% CI, −0.65 to 0.29; P=0.42). A combination of major bleeding and clinically relevant nonmajor bleeding occurred in 22 patients (1.29%) in the aspirin group and in 17 (0.99%) in the rivaroxaban group (difference, 0.30 percentage points; 95% CI, −1.07 to 0.47; P=0.43). All bleeding events consisted of overt hemorrhage at the surgical site. Most bleeding events took place within 10 days after randomization. One death from pulmonary embolism occurred in the aspirin group in a patient who had undergone total knee arthroplasty. The death occurred 31 days after randomization and 17 days after the completion of aspirin prophylaxis. There were no other deaths during the trial.
Eriksson et al.[65] (2008) RECORD1 Rivaroxaban 10 mg QD for 35 days	DB, DD, MC, RCT Patients ≥18 years of age undergoing elective total hip replacement	N=4,541 70 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause up to 36	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint (1.1 vs 3.7%; ARR, -2.6%; 95% CI, -3.7 to -1.5; P<0.001). There was no difference between rivaroxaban and enoxaparin for major bleeding events (0.3 vs 0.1%; P=0.18).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs enoxaparin 40 mg SC QD in the evening for 35 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was administered 12 hours prior to surgery and then reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.			days; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow-up, death during the follow-up period, any on-treatment bleeding, any on-treatment nonmajor bleeding, hemorrhagic wound complications, any bleeding that	Secondary: Rivaroxaban significantly reduced the risk of major VTE (0.2 vs 2.0%; ARR, -1.7%; 95% CI, -2.5 to 1.0; P<0.001). Rivaroxaban significantly reduced the risk of DVT (0.8 vs 3.4%; ARR, -2.7; 95% CI, -3.7 to -1.7; P<0.001). Rivaroxaban and enoxaparin had similar rates of symptomatic VTE during treatment (0.3 vs 0.5%; ARR, -0.2%; 95% CI, -0.6 to 0.1; P=0.22) and follow-up (<0.1 vs 0.0%; ARR, -0.1%; 95% CI, -0.4 to 0.1; P=0.37). Both treatments had <0.1% cases of death occurring during follow-up (P value not reported). Rivaroxaban and enoxaparin had similar rates for any on-treatment bleeding (6.0 vs 5.9%; P=0.94) and any on-treatment nonmajor bleeding events (5.8 vs 5.8%; P value not reported). The rate of hemorrhagic wound complications was also similar (1.5 vs 1.7%; P value not reported). The rate of any bleeding beginning after the first dose of rivaroxaban or placebo were also similar (5.5 vs 5.0%; P value not reported). Rivaroxaban and enoxaparin had similar rates of any on-treatment adverse event (64.0 vs 64.7%; P value not reported). The incidence of death during the on-treatment period was similar between the two treatments (0.3 vs 0.3%; ARR, 0%; 95% CI, -0.4 to 0.4; P=1.00). Of the four deaths that occurred with rivaroxaban, two were possibly related to VTE. Of the four deaths that occurred with enoxaparin, one was related to VTE.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			started after the first dose and up to two days after the last dose of the study drug, adverse events and death	
Kakkar et al.[66] (2008) RECORD2 Rivaroxaban 10 mg QD for 31 to 39 days vs enoxaparin 40 mg SC QD for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was administered 12 hours prior to surgery and reinitiated six to eight hours after wound closure. All patients received either placebo tablets or	DB, DD, MC, RCT Patients ≥18 years of age undergoing complete hip replacement	N=2,509 75 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause up to day 30 to 42; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE, (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (2.0 vs 9.3%; ARR, 7.3%; 95% CI, 5.2 to 9.4; P<0.0001). Major bleeding occurred at a rate <0.1% with both rivaroxaban and enoxaparin (P value not reported). The one major bleeding event with enoxaparin was deemed unrelated to the treatment drug by the adjudication committee. Secondary: Rivaroxaban significantly reduced the risk of major VTE (0.6 vs 5.1%; ARR, 4.5%; 95% CI, 3.0 to 6.0; P<0.0001). Rivaroxaban significantly reduced the risk of DVT (1.6 vs 8.2%; ARR, 6.5%; 95% CI, 4.5 to 8.5; P<0.0001). Rivaroxaban significantly reduced the risk of on-treatment symptomatic VTE (0.2 vs 1.2%; ARR, 1.0%; 95% CI, 0.3 to 1.8; P=0.004); however, the rates during follow-up were similar (0.1 vs 0.2%; ARR, 0.1%; 95% CI, -0.2 to 0.4; P=0.62). The incidence of death during the follow-up period was similar between the two treatments (0.0 vs 0.2%; ARR, 0.2%; 95% CI, -0.1 to 0.6; P=0.50). Rates of any on-treatment bleeding (6.6 vs 5.5%; P value not reported) and any on-treatment nonmajor bleeding (6.5 vs 5.5%; P value not reported) were similar between the two treatments. Hemorrhagic wound complications also occurred at similar rates (1.6 vs 1.7%; P value not reported). The rate of any bleeding beginning after initiation of rivaroxaban or placebo was also similar (4.7 vs 4.1%; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo injection.			VTE during treatment and follow-up, death during the follow-up period, any on-treatment bleeding, any on-treatment nonmajor bleeding, hemorrhagic wound complications, any postoperative bleeding that started after the first dose and up to two days after the last dose of the study drug, adverse events and death	Adverse events from any cause were similar between the two treatments (62.5 vs 65.7%; P values not reported). The incidence of on-treatment death was similar between the two treatments (0.2 vs 0.7%; ARR, 0.5%; 95% CI, -0.2 to 1.1; P=0.29).
Lassen et al.[67] (2008) RECORD3 Rivaroxaban 10 mg QD for 10 to 14 days vs enoxaparin 40 mg SC QD for 10 to 14 days	DB, DD, MC, RCT Patients ≥18 years of age undergoing elective total knee replacement	N=2,531 49 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause within 13 to 17 days post surgery; incidence of major bleeding beginning after the first dose of the study drug	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (9.6 vs 18.9%; ARD, -9.2%; 95% CI, -12.4 to -5.9; P<0.001). The rate of major bleeding was similar between the two treatments (0.6 vs 0.5%; P=0.77). Secondary: Rivaroxaban significantly reduced the risk of major VTE (1.0 vs 2.6%; ARD, -1.6%; 95% CI, -2.8 to -0.4; P=0.01). Rivaroxaban significantly reduced the risk of DVT (9.6 vs 18.2%; ARD, -8.4;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin as administered 12 hour preoperatively and reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.			and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow up, death during the follow up period, any on-treatment bleeding or any major bleeding occurring between intake of the first dose of the study medication and two days after the last dose, nonmajor bleeding, adverse events and death	95% CI, -11.7 to -5.2; P<0.001). Rivaroxaban significantly reduced the risk of on-treatment symptomatic VTE (0.7 vs 2.0%; ARD, -1.3%; 95% CI, -2.2 to -0.4; P=0.005); however, during follow-up the rates were similar (0.4 vs 0.2%; ARD, 0.2%; 95% CI, -0.3 to 0.6; P=0.44). The incidence of death during follow-up was similar between the two treatments (ARD, -0.2%; 95% CI, -0.6 to 0.2; P=0.21). Rates of any on-treatment bleeding (4.9 vs 4.8%; P=0.93) or any major bleeding between the start of treatment and two days after the last dose (0.6 vs 0.5%; P=0.77) were similar between the two treatments. The rate of nonmajor bleeding was also similar (4.3 vs 4.4%; P value not reported). The rates of drug-related adverse events were similar between the two treatments (12 vs 13%; P value not reported). The incidence of death during treatment was similar between the two treatments (0.0 vs 0.2%; ARD, -0.2%; 95% CI, -0.8 to 0.2; P=0.23)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Turpie et al.[68] (2009) RECORD4 Rivaroxaban 10 mg QD for 10 to 14 days vs enoxaparin 30 mg SC BID for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was initiated 12 to 24 hours after wound closure. All patients received either placebo tablets or placebo injection.	DB, DD, MC, RCT Patients ≥18 years of age undergoing total knee replacement	N=3,148 49 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause 17 days after surgery; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of asymptomatic DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow up, death during the follow-up period, clinically	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (6.9 vs 10.1%; ARD, -3.19%; 95% CI, -5.67 to -0.71; P=0.0118). There was no difference in the rate of major bleeding between the two treatments (0.7 vs 0.3%; P=0.1096). Secondary: Rivaroxaban did not reduce the risk of major VTE compared to enoxaparin (1.2 vs 2.0%; ARD, -0.80; 95% CI, -1.34 to 0.60; P=0.1237). The rates of asymptomatic DVT were similar between the two treatments (P value not reported). Rivaroxaban did not reduce the risk of symptomatic VTE on-treatment (0.7 vs 1.2%; ARD, -0.47; 95% CI, -1.16 to 0.23; P=0.1868) or during follow-up (0.2 vs 0.2%; ARD, 0.00%; 95% CI, -0.32 to 0.32; P=0.9979). The incidence of death during follow-up was similar between the two treatments (0.3 vs 0.2%; ARD, 0.06%; 95% CI, -0.35 to 0.50; P=0.8044). The rates of clinically relevant nonmajor bleeding (10.2 vs 9.2%; P value not reported) and any on-treatment bleeding (10.5 vs 9.4%; P=0.3287) were similar between the two treatments. The rate of hemorrhagic wound complications was also similar (1.4 vs 1.5%; P value not reported). The rates of drug-related adverse events were similar between the two treatments (20.3 vs 19.6%; P value not reported). The rates of on-treatment death were similar between the two treatments (0.1 vs 0.2%; P=0.7449).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			relevant nonmajor bleeding, any on-treatment bleeding, any nonmajor bleeding, hemorrhagic wound complications, adverse events and death	
Hutten et al.[69] (2006) Oral anticoagulants (dicoumarol*, warfarin) Trials were included if different durations of treatment with a VKA were compared. The eight trials compared seven different periods of treatment with VKAs: four weeks vs three months, six vs 12 weeks, six weeks vs six months, three vs six months, three	SR (8 trials) Patients with symptomatic VTE	N=2,994 Duration varied	Primary: Recurrent VTE Secondary: Major bleeding, mortality	Primary: All trials reported on the occurrence of symptomatic VTE during the period from cessation in VKA-treated patients in the short duration arm until cessation of treatment in the long duration arm. Four trials demonstrated a significant protection from recurrent VTE complications during prolonged treatment with VKAs, while the others revealed a clear trend. In the combined analysis of all eight trials, a significant reduction in thromboembolic events during prolonged treatment was observed (116 out of 1,495 short duration vs 14 out of 1,499 long duration; OR, 0.18; 95% CI, 0.13 to 0.26). Six trials evaluated the incidence of recurrent VTE in the period after cessation of study medication. No trial demonstrated a significant increase in VTE events among participants in the long arm after cessation of treatment, and combined analysis demonstrated similar results (96 out of 1,304 long duration vs 78 out of 1,301 short duration; OR, 1.24; 95% CI, 0.91 to 1.69). Analyses of pooled data demonstrated a significant reduction in recurrent VTE for the following comparisons: four weeks vs three months (OR, 0.23; 95% CI, 0.06 to 0.70), three vs six months (OR, 0.13; 95% CI, 0.05 to 0.33) and three vs 12 months (OR, 0.22; 95% CI, 0.11 to 0.44). Secondary: Four trials reported the incidence of major bleeding during the period from cessation of treatment with VKAs in the short duration arm until cessation of treatment in the long duration arm. No trial demonstrated a significant increase

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months vs one year, three vs 27 months, and six months vs four years.				in bleeding complications during prolonged treatment, but combined results demonstrated a significant increase in major bleeding complications during this period (one out of 405 short duration vs eight out of 403 long duration; OR, 4.87; 95% CI, 1.31 to 18.15). Only one trial reported the incidence of major bleeding in the period after cessation of study medication. All trials reported on the occurrence of major bleeding complications for the entire period after randomization until the end of follow-up. No trial demonstrated a significant increase during prolonged treatment, but combined results demonstrated a significant increase during this period (36 out of 1,499 long duration vs 13 out of 1,495 short duration; OR, 2.61; 95% CI, 1.48 to 4.61). Three trials reported mortality during the period from cessation of treatment with VKAs in the short duration arm until cessation of treatment in the long duration arm. One trial demonstrated a non-significant decrease in mortality during prolonged treatment, while the others showed no trends. Combined results demonstrated a non-significant reduction in mortality favoring prolonged treatment (12 out of 188 short duration vs 10 out of 188 long duration; OR, 0.80; 95% CI, 0.34 to 1.91). All trials reported on mortality for the entire period after randomization, with none demonstrating a significant reduction in morality. When the results were combined, a nonsignificant reduction in mortality during the entire study period was observed (71 out of 1,498 long duration vs 75 out of 1,496 short duration; OR, 0.93; 95% CI, 0.67 to 1.30).
van der Heijden et al.[70] (2001) VKAs vs LMWH	SR (7 RCTs) Patients with symptomatic DVT receiving long-term treatment	N=1,137 3 to 9 months	Primary: Recurrent symptomatic VTE, major bleeding complications, mortality Secondary: Not reported	Primary: All seven trials reported the occurrence of recurrent symptomatic VTE during the first three to six months after randomization. Six trials showed no differences between treatment with LMWH and VKAs, and one trial found a significant OR of 0.38 (95% CI, 0.17 to 0.86) in favor of treatment with LMWH. When the seven trials are combined, the rate of recurrent symptomatic VTE was 6.7 vs 4.8% in VKA- and LMWH-treated patients, corresponding to a nonsignificant reduction in favor of LMWH (OR, 0.70; 95% CI, 0.42 to 1.16). Six trials evaluated the occurrence of recurrent symptomatic VTE during a period of six to nine months after cessation of the allocated treatment. The rate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of recurrent symptomatic VTE was 3.5 vs 5.0% of VKA- and LMWH-treated patients, corresponding to nonsignificant difference in favor of VKA treatment (OR, 1.46; 95% CI, 0.80 to 2.69). All seven trials reported the incidence of major bleeding during allocated treatment, with six trials finding no difference between the two treatments and one finding a significant difference in favor of treatment with LMWH (OR, 0.12; 95% CI, 0.02 to 0.89). When the trials were combined, 2.5 vs 0.9% VKA- and LMWH-treated patients had a major bleed; a significant difference in favor of treatment with LMWH (OR, 0.38; 95% CI, 0.15 to 0.94). No major bleeding occurred in the additional nine months of follow-up. All seven trials reported on mortality during the allocated treatment, with the individual trials not finding a significant difference between the two treatments. In the combined analysis, 2.5 vs 3.7% of VKA- and LMWH-treated patients died (OR, 1.51; 95% CI, 0.77 to 2.97). Six trials extended the follow-up period for an additional six to nine months and found that the rate of death was 3.5 vs 3.9% (OR, 1.11; 95% CI, 0.58 to 2.15). Secondary: Not reported
Salazar et al.[71] (2010) DTI (dabigatran†, desirudin, ximelagatran*) vs warfarin or LMWH (dalteparin, enoxaparin)	SR (12 RCTs) Patients who have undergone total hip replacement or total knee replacement	N=21,642 (efficacy) N=27,360 (safety) Duration varied	Primary: Mortality associated with VTE, incidence of proximal VTE, mortality associated with treatment, appearance of serious hepatopathy, appearance of other serious adverse effects associated with treatment	Primary and Secondary end points are reported together in the groupings below. *Major, total and symptomatic VTE* Combined analysis from two trials comparing DTIs to LMWH demonstrated that when evaluating the combination of both surgery groups, no difference was observed between the two treatments (557 out of 10,736 vs 392 out of 6,692 events/patients; OR, 0.91; 95% CI, 0.69 to 1.19). Evaluation of the individual surgery groups had similar results. No difference was observed between the two treatments for total VTE (data not reported) or symptomatic VTE (234 out of 12,056 vs 143 out of 7,563; OR, 1.04; 95% CI, 0.84 to 1.29). Combined analysis from three trials comparing ximelagatran to warfarin demonstrated no statistical difference between the two treatments (95 out of 2,498 vs 83 out of 1,829 events/patients; OR, 0.85; 95% CI, 0.63 to 1.15). There were fewer total VTE events in DTI-treated patients (555 out of 2,514 vs 543 out of 1,840; OR, 0.68; 95% CI, 0.59 to 0.78). No difference between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Incidence of distal VTE, presence of hepatopathy after treatment, morbidity associated with treatment	two treatments were observed for symptomatic VTE (47 out of 3,022 vs 48 out of 2,237; OR, 0.80; 95% CI, 0.53 to 1.21). *Major/significant and total bleeding events* Combined analysis from eleven trials comparing DTIs to LMWH demonstrated a nonsignificant higher number of major significant bleeding events in DTI-treated patients (334 out of 13,753 vs 138 out of 8,356 events/patients; OR, 1.17; 95% CI, 0.87 to 1.58). In the comparison of each independent dose, only dabigatran 225 mg BID showed more bleeding events in the DTI group (OR, 1.90; 95% CI, 1.05 to 3.44) in the combination of both surgeries and specifically in total hip replacement (26 out of 270 vs 13 out of 270; OR, 2.11; 95% CI, 1.06 to 4.19). Combined analysis from ten trials demonstrated no difference between the two treatments in terms of total bleeding events; however, more events were observed in DTI-treated patients undergoing total hip replacement (2,370 out of 5,949 vs 1,374 out of 4,378; OR, 1.40; 95% CI, 1.06 to 1.85). Combined analysis of three trials comparing ximelagatran to warfarin demonstrated more major/significant bleeding events with ximelagatran, but the difference was not statistically significant (30 out of 3,022 vs 13 out of 2,237 events/patients; OR, 1.76; 95% CI, 0.91 to 3.38). Partial and total bleeding events were very similar to major bleeding events. *All-cause mortality* Combined analysis of eleven trials comparing DTIs to LWMH demonstrated a nonsignificant higher all-cause mortality event rate with DTI treatment (15 out of 13,730 vs four out of 8,335 events/patients; OR, 1.72; 95% CI, 0.68 to 4.35). When including follow-up events the difference met statistical significance (41 out of 13,730 vs 11 out of 8,335; OR, 2.06; 95% CI, 1.10 to 3.87). Combined analysis of three trials comparing ximelagatran to warfarin demonstrated no significant difference between the two treatments (six out of 3,013 vs four out of 2,230 events/patients; OR, 1.19; 95% CI, 0.36 to 4.01), even when follow-up events were included (10 out of 3,013 vs five out of 2,230; OR, 1.62; 95% CI, 0.57 to 4.58). *ALT greater than three times the upper normal limit*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The seven trials comparing DTIs to LMWH had high heterogeneity; therefore, results could not be combined. Fewer events were observed in DTI-treated patients, but with high heterogeneity, in the ximelagatran trials. No difference was noted when treatment with dabigatran was compared to treatment with LMWH, but these trials had very high heterogeneity. Combined analysis of two trials comparing ximelagatran to warfarin demonstrated no significant difference between the two treatments (18 out of 2,493 vs 21 out of 1,768 events/patients; OR, 0.52; 95% CI, 0.27 to 0.97), even when follow-up events were included (11 out of 2,484 vs one out of 1,783; OR, 5.61; 95% CI, 1.00 to 31.64). *Volume of blood loss* No difference was observed between treatment with DTIs and LMWH in the combined analysis of five trials (n=8,782; WMD, 5.12; 95% CI, -33.81 to 44.04), but these trials had high heterogeneity. No difference was observed between ximelagatran and warfarin in the combined analysis of three trials (n=5,259; WMD, -7.12; 95% CI, -17.08 to 2.84), with no heterogeneity. *Time effect of the beginning of anticoagulation* Trials comparing DTIs to LMWH that began anticoagulation before surgery demonstrated fewer major (OR, 0.54; 95% CI, 0.35 to 0.83) and total (OR, 0.72; 95% CI, 0.63 to 0.82) VTE in DTI-treated patients in both surgery groups. There was also no difference regarding symptomatic VTE. Trials that began anticoagulation after surgery demonstrated more major (OR, 1.68; 95%, 1.12 to 2.52) and total (OR, 1.29; 95% CI, 0.69 to 2.39) VTE events in DTI-treated patients in both surgery groups. Again, there was no difference regarding symptomatic VTE. Trials that began anticoagulation before surgery demonstrated a non- significant greater incidence of major (OR, 1.64; 95% CI, 0.85 to 3.15) and total (OR, 1.45; 95% CI, 0.93 to 2.28) bleeding events in DTI-treated patients in both combined surgeries and in the individual analysis of each surgery. There was no significant difference regarding mortality.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Extended prophylactic anticoagulation vs standard prophylactic anticoagulation No difference was found in major or total VTE between DTI- and LMWH-treated patients. Symptomatic VTE events in extended anticoagulation occurred more with dabigatran in comparison to LMWH, but the difference was not statistically significant (25 out of 2,293 vs five out of 1,142 events/patients; OR, 2.51; 95% CI, 0.96 to 5.67). In standard anticoagulation, no difference between DTI- and LMWH-treated patients was noted (76 out of 3,351 vs 37 out of 1,542; OR, 0.99; 95% CI, 0.67 to 1.48). Regarding safety, no difference in major or total bleeding events was noted. All-cause mortality, transaminase levels and blood loss were not evaluated.
Jun et al.[72] (2017) CNODES Direct oral anticoagulant (apixaban, dabigatran, or rivaroxaban) vs warfarin	Cohort, RETRO Adults with a new diagnosis of VTE and a prescription for a direct oral anticoagulant or warfarin within 30 days of diagnosis	N=59,525 Mean follow-up of 85.2 days	Primary: Time to an incident major bleed (defined as first hospital admission or emergency department visit for intracranial, gastrointestinal, or other bleeding in the 90 days after cohort entry) Secondary: All cause mortality in the 90 days after cohort entry	Primary: Over a mean follow-up of 85.2 days, 3.3% of patients had a major bleed, of which 6.7%, 38.7%, and 54.6% were due to an intracranial, gastrointestinal, and other bleed, respectively. Bleeding rates at 30 days ranged between 0.2% and 2.9% for direct oral anticoagulants and 0.2% and 2.9% for warfarin. Bleeding rates at 60 days ranged between 0.4% and 4.3% for direct oral anticoagulants and 0.4% and 4.3% for warfarin. Overall, the risk of major bleeding associated with direct oral anticoagulant use among patients with incident venous thromboembolism was similar to that with warfarin use (HR, 0.92; 95% CI, 0.82 to 1.03), with the direction of the association favoring direct oral anticoagulants. Secondary: No difference was found in the risk of death (pooled HR, 0.99; 95% CI, 0.84 to 1.16) for direct oral anticoagulants compared with warfarin use.
Brookenthal et al.[73] (2001)	MA (14 trials) Patients receiving	N=3,482 Duration	Primary: Total DVT, proximal DVT,	Primary: For total DVT, all treatments, except dextran and aspirin, protected significantly better than placebo (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Thromboprophyl-axis (aspirin, dextran, heparin [with or without antithrombin III], LMWH [ardeparin*, enoxaparin, tinzaparin], lower extremity pneumatic compression stockings, or warfarin) vs placebo A prophylactic agent of interest was compared to another method of interest or placebo.	prophylaxis for ≥7 days for an elective total knee arthroplasty	varied	distal DVT, symptomatic PE, fatal PE, minor bleeding, major bleeding, total bleeding, intracranial hemorrhage, non-PE mortality, all-cause mortality Secondary: Not reported	For proximal DVT, no comparison against placebo was available, and rates ranged from 1.7 (aspirin) to 12.8% (SC heparin/antithrombin III). The only significant difference was between treatment with LMWH and warfarin (5.9 vs 10.2%; P=0.0002). There was a strong trend that aspirin protected better than warfarin (1.7 vs 10.2%; P=0.0106). For distal DVT, no comparison against placebo was available. LMWH (24.4%) protected significantly better than dextran (71.1%; P=0.0001), warfarin (35.6%; P=0.0001) and aspirin (55.2%; P=0.0001). Warfarin (35.6%) protected significantly better than aspirin (55.2%; P=0.0045) but worse than SC heparin (21.5%; P=0.0029). Aspirin (55.2%) protected significantly less than SC heparin (21.5%; P=0.0001) and pneumatic compression stockings (29.5%; P=0.0051). Rates of symptomatic PE ranged from 0.0 (aspirin, pneumatic compression stockings and placebo) to 0.4% (warfarin, SC heparin); there was no significant detectable difference among the agents. No fatal PE occurred with any treatment. The rate of total bleeding ranged from 8.6 (aspirin) to 18.9% (SC heparin). No comparison with placebo was available. The rate of minor bleeding ranged from 8.6 (aspirin) to 18.3% (SC heparin). Rates of major bleeding ranged from 0.0 (aspirin, pneumatic compression stockings) to 2.4% (LWMH), but no difference between treatments were noted. There were no observed intracranial hemorrhages. Rates for overall and non-PE mortality ranged from 0.0 (aspirin, SC heparin, pneumatic compression stockings, placebo, SC heparin/antithrombin III and dextran) to 0.3% (warfarin), but no difference among the treatments were noted. Secondary: Not reported
Cundiff et al.[74] (2006) Anticoagulants	SR (2 RCTs) Patients with DVT or PE	N=113 3 months	Primary: Mortality due to PE, PE, DVT and extension of DVT	Data were not pooled because of heterogeneity between the trials, and the trials were too small to determine any difference in mortality, occurrence of PE, and progression or return of DVT between patients receiving anticoagulation and those who were not.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(heparin, phenprocoumon*, warfarin) vs NSAIDs (phenylbutazone*) or placebo			or both Secondary: All-cause mortality, major hemorrhagic events, fatal hemorrhagic events, morbidity and mortality due to HIT with thrombosis	Primary: In one trial (n=23), no deaths due to PE were reported and in the other trial (n=90), there was no significant difference in deaths due to PE between anticoagulant- and NSAID-treated patients (one vs zero; RR, 2.63; 95% CI, 0.11 to 62.95). In one trial (n=23), there was no difference in the combined outcome PE, DVT progression or return in anticoagulation-treated patients compared to those who did not receive anticoagulation (five vs five; RR, 1.09; 95% CI, 0.43 to 2.77). In one trial (n=90), there was no difference in the combined outcome recurrent DVT or DVT (18 vs 22; RR, 0.72; 95% CI, 0.45 to 1.14). Secondary: There was no difference in the secondary outcomes of all-cause mortality and major hemorrhage in either trial between the two treatments. Neither trial reported morbidity or mortality due to HIT with thrombosis, or VKA necrosis.
Di Nisio et al.[75] (2012) Any oral or parenteral anticoagulant (UFH, LMWH, VKA, direct thrombin or factor Xa inhibitors), or both vs inactive control (placebo, no treatment, standard care) or active	SR (9 RCTs) Ambulatory outpatients of any age with either a solid or hematological cancer, at any stage, and receiving chemotherapy, without a positive history of VTE	N=3,538 Duration varied	Primary: Symptomatic VTE, major bleeding Secondary: Symptomatic PE, symptomatic DVT, asymptomatic VTE, overall VTE, minor bleeding, one year overall mortality, arterial thromboembolic events,	Primary: LMWH vs inactive control Pooled analysis of six RCTs demonstrated that when compared to placebo, LMWH was associated with a significant reduction symptomatic VTE (RR, 0.62; 95% CI, 0.41 to 0.93), corresponding to a NNT of 60. Pooled analysis of six RCTs suggested a 60% increased risk of a major bleeding (RR, 1.57; 95% CI, 0.69 to 3.60). LMWH vs active control In one trial, LMWH was associated with a 67% reduction in symptomatic VTE relative to warfarin (RR, 0.33; 95% CI, 0.14 to 0.83) while the difference with aspirin was not significant (RR, 0.50; 95% CI, 0.19 to 1.31). In one trial, there were no differences between LMWH, aspirin, and warfarin regarding the incidence of major bleeding. VKA vs inactive control

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
control			superficial thrombophlebitis, quality of life, number of patients experiencing any serious adverse event	In one trial, a trend for a reduction in symptomatic VTE (RR, 0.15; 95% CI, 0.02 to 1.20) was reported. There was no significant effect on major bleeding (RR, 0.52; 95% CI, 0.05 to 5.71). VKA vs active control One trial reported a nonsignificant difference between VKA and aspirin (RR, 1.50; 95% CI, 0.74 to 3.04). Antithrombin vs inactive control In one trial, the effects of antithrombin on symptomatic VTE (RR, 0.84; 95% CI, 0.41 to 1.73) and major bleeding (RR, 0.78; 95% CI, 0.03 to 18.57) were not significant. Secondary: LMWH vs inactive control Pooled analysis of six RCTs demonstrated that there was no significant effect on symptomatic PE (RR, 0.63; 95% CI, 0.21 to 1.91) or DVT (RR, 0.60; 95% CO. 0.33 to 1.07). In pooled data from six RCTs, the risk of overall VTE was reduced by 45% with LMWH (RR, 0.55; 95% CI, 0.34 to 0.88) whereas there was no significant benefit or harm for asymptomatic VTE, minor bleeding, one-year mortality, symptomatic arterial thromboembolism, superficial thrombophlebitis, or serious adverse events. None of the six trials considered quality of life, heparin-induced thrombocytopenia, or the incidence of osteoporosis as study incomes. Three trials reported on symptomatic VTE and major bleeding in patient with non-small cell or small cell lung cancer, or both. Pooled analysis showed a nonsignificant 46% reduction in symptomatic VTE (RR, 0.54; 95% CI, 0.27 to 1.09) and a nonsignificant 73% higher risk of major bleeding with LMWH compared to control (RR, 1.73; 95% CI, 0.65 to 4.57). LMWH vs active control In one trial, there were no differences between LMWH, aspirin, and warfarin regarding the incidence of symptomatic PE or DVT, minor bleeding, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				symptomatic arterial thromboembolism. VKA vs inactive control In one trial, there was no significant effect on symptomatic PE (RR, 1.05; 95% CI, 0.07 to 16.58), symptomatic DVT (RR, 0.08; 95% CI, 0.00 to 1.42), or minor bleeding (RR, 2.44; 95% CI, 0.64 to 9.27). No symptomatic arterial thromboembolic events were observed in the VKA or placebo groups. VKA vs active control and antithrombin vs inactive control Secondary outcomes were not reported for these comparisons.
Castellucci et al.[76] (2014) Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux in combination with vitamin K antagonists; LMWH with dabigatran or edoxaban*; rivaroxaban; apixaban; and LMWH alone	SR and MA (45 trials) Patients who had objectively confirmed symptomatic acute VTE (lower extremity DVT, pulmonary embolism, or both) and who had qualifying recurrent VTE events that were symptomatic and objectively confirmed	N=44,989 Duration varied	Primary: Recurrent VTE and major bleeding Secondary: Fatal recurrent VTE and fatal bleeding episodes	Primary: Compared with the LMWH–vitamin K antagonist combination, use of the UFH–vitamin K antagonist combination in patients with index deep vein thrombosis was associated with the lowest efficacy and was associated with an increased risk of recurrent venous thromboembolism (HR, 1.74; 95% credible interval [CrI], 1.27 to 2.44). All remaining treatment regimens were not associated with differences in outcomes from the LMWH–vitamin K antagonist combination in this population. Compared with the LMWH–vitamin K antagonist combination, rivaroxaban (HR, 0.55; 95% CrI, 0.35 to 0.89) and apixaban (HR, 0.31; 95% CrI, 0.15 to 0.62) were associated with the lowest bleeding risk. All other treatment regimens were associated with bleeding risks that did not differ from the LMWH–vitamin K antagonist combination. Secondary: Fatal events were rare. One hundred sixty-five patients (0.37%) experienced fatal recurrent venous thromboembolism and 64 (0.14%), fatal bleeding events.
Schulman et al.[77] (2009) RE-COVER Dabigatran 150 mg BID vs	DB, DD, MC, RCT Patients ≥ 18 years of age with acute symptomatic, objectively verified proximal DVT thrombosis of the legs or PE and for	N= 2,539 6 months	Primary: Time to the first occurrence of symptomatic VTE or death associated with VTE Secondary:	Primary: After central adjudication, the primary outcome for efficacy was confirmed in 30 patients in the dabigatran group (2.4%) and 27 patients in the warfarin group (2.1%). The difference in risk was 0.4% (95% CI; −0.8 to 1.5; HR, 1.10; 95% CI, 0.65 to 1.84). As compared with warfarin, dabigatran was noninferior with regard to the prevention of recurrent or fatal VTE (P<0.001 for the criteria of both HR and the difference in risk). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Warfarin dose adjusted QD All patients received parenteral anticoagulation for a mean of 10 days	who six months of anticoagulant therapy was considered to be an appropriate treatment		Symptomatic DVT, symptomatic nonfatal PE, death related to VTE, all deaths	Symptomatic DVT occurred in 16 patients in the dabigatran group (1.3%) and 18 patients in the warfarin group (2.1%), HR 0.87 (95% CI; 0.44 to 1.71). Symptomatic nonfatal PE occurred in 13 patients in the dabigatran group (1.0%) and 7 patients in the warfarin group (0.6%), HR 1.85 (95% CI; 0.74 to 4.64). Death related to VTE occurred in one patient in the dabigatran group (0.1%) and three patients in the warfarin group (0.3%), HR 0.33 (95% CI; 0.03 to 3.15). All deaths occurred in 21 patients in the dabigatran group (1.6%) and 21 patients in the warfarin group (1.7%), HR 0.98 (95% CI; 0.53 to 1.79).
Schulman et al.[78] (2014) RE-COVER II Dabigatran 150 mg BID vs warfarin dose adjusted QD All patients received five to 11 days of therapy with LMWH or unfractionated heparin	DB, DD, MC, RCT Patients ≥ 18 years of age with acute symptomatic, objectively verified proximal DVT thrombosis of the legs or PE and for who six months of anticoagulant therapy was considered to be an appropriate treatment	N=2,589 6 months	Primary: Recurrent symptomatic, objectively confirmed VTE and related deaths during six months of treatment. Secondary: Symptomatic DVT, symptomatic non-fatal PE, death related to PE, and all death	Primary: Recurrent non-fatal or fatal VTE was confirmed after central adjudication in 30 patients in the dabigatran group (2.3%) and in 28 patients in the warfarin group (2.2%; HR, 1.08; 95% CI, 0.64 to 1.80). The difference in risk was 0.2% (95% CI, −1.0 to 1.3) in favor of warfarin. Dabigatran was non-inferior to warfarin for the prevention of recurrent or fatal VTE (P<0.001 for both HR and difference in absolute risk criteria). Efficacy results were consistent in all the predefined subgroups (data not shown). Secondary: Symptomatic DVT occurred in 25 patients (2.0%) in the dabigatran group and 2.2 patients (1.3%) in the warfarin group (HR, 1.08; 95% CI, 0.80 to 2.74). Symptomatic nonfatal PE occurred in seven patients (0.5%) in the dabigatran group and 13 (1.0%) patients in the warfarin group (HR, 0.54; 95% CI, 0.21 to 1.35). There occurred that were related to PE in the dabigatran group with zero in the warfarin group. There were 25 deaths (2.0%) in the dabigatran group and 25 deaths (1.9%) in the warfarin group (HR, 0.98; 95% CI, 0.56 to 1.71)
Schulman et al.[79] (2013) Study 1: RE-MEDY Dabigatran 150 mg BID vs warfarin (dose	Study 1: AC, DB, MC, NI, RCT Study 2: PC, DB, MC, RCT Patients ≥18 years of age diagnosed with VTE who completed at least	N= 4,199 6 to 36 months	Primary: Recurrent symptomatic and objectively verified VTE or death associated with VTE (or unexplained death in the placebo-control study), major	Primary: In the active-control study, recurrent VTE occurred in 26 of 1,430 patients in the dabigatran group (1.8%) and 18 of 1426 patients in the warfarin group (1.3%) (HR, 1.44; 95% CI, 0.78 to 2.64; P=0.01 for noninferiority). Major bleeding occurred in 13 patients in the dabigatran group (0.9%) and 25 patients in the warfarin group (1.8%) (HR, 0.52; 95% CI, 0.27 to 1.02). Major or clinically relevant bleeding was less frequent with dabigatran (HR, 0.54; 95% CI, 0.41 to 0.71). Acute coronary syndromes occurred in 13 patients in the dabigatran group (0.9%) and three patients in the warfarin group (0.2%) (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adjusted) QD Study 2: RE-SONATE Dabigatran 150 mg BID vs placebo	the first three months of therapy (six months for the second study)		bleeding and clinically relevant non-major bleeding Secondary: Not reported	In the placebo-control study, recurrent venous thromboembolism occurred in three of 681 patients in the dabigatran group (0.4%) and 37 of 662 patients in the placebo group (5.6%) (HR, 0.08; 95% CI, 0.02 to 0.25; P<0.001). Major bleeding occurred in two patients in the dabigatran group (0.3%) and 0 patients in the placebo group. Major or clinically relevant bleeding occurred in 36 patients in the dabigatran group (5.3%) and 12 patients in the placebo group (1.8%) (HR, 2.92; 95% CI, 1.52 to 5.60). Acute coronary syndromes occurred in one patient each in the dabigatran and placebo groups. Secondary: Not reported
Lassen et al.[80] (2009) ADVANCE-1 Apixaban 2.5 mg BID and matching placebo injection vs enoxaparin 30 mg SC every 12 hours and matching placebo tablets BID Patients received the first doses of the study medications 12 to 24 hours after surgery in order to be consistent with	AC, DB, DD, MC, RCT Patients who were to undergo total knee replacement surgery for one or both knees, including revision of a previously inserted artificial joint	N=3,195 10 to 14 days of treatment (plus 60 days follow-up)	Primary: Composite of asymptomatic and symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, and death from any cause during the intended treatment period Secondary: Composite of major thromboembolism and death from any cause, and symptomatic thromboembolism during the intended	Primary: The statistical criterion for the noninferiority of apixaban as compared with twice-daily administration of enoxaparin was not met. The primary efficacy outcome occurred in 104 of 1157 patients (9.0%) in the apixaban group, as compared with 100 of 1130 patients (8.8%) in the enoxaparin group (RR, 1.02; 95% CI, 0.78 to 1.32; P=0.06 for noninferiority; difference in risk, 0.1%; 95% CI, –2.2% to 2.4%; P<0.001). Secondary: Composite major thromboembolism and death from any cause occurred in 26 of 1269 patients (2.1%) in the apixaban group and in 20 of 1216 patients (1.6%) in the enoxaparin group (RR, 1.25; 95% CI, 0.70 to 2.23; difference in risk, 0.36%; 95% CI, –0.68% to 1.40%). Symptomatic thromboembolism and death from any cause occurred in 26 of 1269 patients (2.1%) in the apixaban group and in 20 of 1216 patients (1.6%) in the enoxaparin group (RR, 1.25; 95% CI, 0.70 to 2.23; difference in risk, 0.36%; 95% CI, –0.68% to 1.40%). Follow-up for 60 days after the last dose of study medication was completed in 1562 of the 1599 patients (97.7%) assigned to apixaban and in 1554 of the 1596 patients (97.4%) assigned to enoxaparin. During the 60-day follow-up period, symptomatic venous thromboembolism occurred in 4 of 1562 patients (0.3%) in the apixaban group and in 7 of 1554 patients (0.5%) in the enoxaparin group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
FDA label for enoxaparin.			treatment period	Major bleeding events occurred in 11 of 1596 patients (0.7%) who received apixaban and in 22 of 1588 patients (1.4%) who received enoxaparin (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49% to −0.14%; P=0.053). The composite outcome of major bleeding and clinically relevant non-major bleeding occurred in 46 patients (2.9%) in the apixaban group and 68 patients (4.3%) in the enoxaparin group (adjusted difference in event rates according to type of surgery, −1.46%; 95% CI, −2.75% to −0.17%; P=0.03).
Lassen et al.[81] (2010) ADVANCE-2 Apixaban 2.5 mg BID and matching placebo injection QD vs enoxaparin 40 mg SC QD and matching placebo tablets BID The first SC injection of study drug was given 12 hours (within three hours) before operation, and injections were resumed after surgery according to investigators' standard of care.	AC, DB, DD, MC, RCT Patients who were scheduled to have unilateral elective total knee replacement or same-day bilateral knee replacement, including revision	N=3,057 10 to 14 days of treatment (plus 60 days follow-up)	Primary: Composite of adjudicated asymptomatic or symptomatic DVT, non-fatal pulmonary embolism, and all-cause death during the intended treatment period or within two days of last dose of study drug, whichever was longer Secondary: Composite major VTE; composite of symptomatic DVT, non-fatal PE and VTE-related death; composite of all DVTs (including asymptomatic);	Primary: Apixaban was had statistically significant reduction in risk compared to enoxaparin for prevention of all VTE and all-cause death (RR, 0.62; 95% CI, 0.51 to 0.74, one-sided P<0.0001 when tested for non-inferiority and for superiority). ARR was 9.3% (95% CI, 5.8% to 12.7%) in favor of apixaban (one-sided p<0·0001 for non-inferiority). Secondary: Apixaban was also provided a statistically significant risk reduction compared with enoxaparin for major VTE prevention (RR, 0.50; 95% CI, 0.26 to 0.97, one-sided P=0.0186 for superiority; ARR, 1.04%; 95% CI, 0.05% to 2.03%). Rates of symptomatic VTE and VTE-related death did not differ between study groups (RR, 1.00; 0.35 to 2.85; ARR, 0.00%; (95% CI, −0.48% to 0.48%). One apixaban patient died of pulmonary embolism during. 1458 (95%) of 1528 apixaban patients and 1469 (96%) of 1529 enoxaparin patients completed 60 days of follow-up after last dose of study drug. Symptomatic venous thromboembolism developed during follow-up in five (<1%) of 1458 apixaban patients and two (<1%) of 1469 enoxaparin patients. There were no statistically significant differences between treatments for the remaining secondary outcomes. Frequency of major bleeding events did not differ between treatment groups (P=0.3014).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
The first dose of oral study drug was given 12 to 24 hours after wound closure.			components of all DVT, including symptomatic DVT, proximal DVT, non-fatal PE, and VTE-related death; composite of PE and VTE-related death; VTE-related death	
Lassen et al.[82] (2010) ADVANCE-3 Apixaban 2.5 mg BID plus matching placebo injection vs enoxaparin 40 mg SC QD plus matching placebo tablets BID The first SC injection of study drug was given 12 hours (within three hours) before operation, and injections were resumed after	AC, DB, DD, MC, RCT Patients who were scheduled to undergo elective total hip replacement or revision of a previously inserted hip prosthesis	N=5,407 32 to 38 days of treatment (plus 95 day follow-up)	Primary: Composite of adjudicated asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause during the intended treatment period Secondary: Major VTE (composite of adjudicated symptomatic or asymptomatic proximal DVT [popliteal, femoral, or iliac-vein thrombosis]), nonfatal PE, or	Primary: The primary efficacy outcome occurred in 27 of the 1949 patients in the apixaban group who could be evaluated for that outcome (1.4%) and in 74 of the 1917 patients in the enoxaparin group who could be evaluated (3.9%) (RR with apixaban, 0.36; 95% CI, 0.22 to 0.54; one-sided P<0.001 for noninferiority and two-sided P<0.001 for superiority). The ARR with apixaban was 2.5% (95% CI, 1.5% to 3.5%). Secondary: Major VTE occurred in 10 of the 2199 patients (0.5%) in the apixaban group who could be evaluated for that outcome and in 25 of the 2195 (1.1%) in the enoxaparin group (RR, 0.40; 95% CI, 0.15 to 0.80; one-sided P<0.001 for noninferiority and two-sided P=0.01 for superiority). The ARR with apixaban was 0.7% (95% CI, 0.2% to 1.3%). With this reduction in risk, one additional episode of VTE would be prevented for every 147 patients treated with apixaban rather than enoxaparin. Major bleeding during the treatment period occurred in 22 of the 2673 patients who received apixaban (0.8%) and 18 of the 2659 patients who received enoxaparin (0.7%) with an absolute difference in risk of 0.1% (95% CI, −0.3% to 0.6%). Thirteen of the 22 major bleeding events in the apixaban group occurred before the first dose was administered; therefore, major bleeding with an onset after the first dose of apixaban occurred in 9 of 2673 patients (0.3%; 95% CI, 0.2% to 0.7%). No bleeding event in either group was related to spinal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
surgery according to investigators' standard of care. The first dose of oral study drug was given 12 to 24 hours after wound closure.			death related to VTE during the intended treatment period	or epidural anesthesia. The composite of major and clinically relevant non-major bleeding occurred in 129 patients who received apixaban (4.8%) and in 134 patients who received enoxaparin (5.0%) with an absolute difference in risk of −0.2% (95% CI, −1.4% to 1.0%). Of the 129 events that occurred in the apixaban group, 33 occurred before the first dose was administered. Thus, major or clinically relevant non-major bleeding with onset after the first dose of apixaban occurred in 96 of the 2673 patients (3.6%; 95% CI, 3.0% to 4.4%).
Weycker et al.[83] (2018) Apixaban vs warfarin	Matched-cohort Patients ≥ 18 years of age who had an encounter for the treatment of VTE and received outpatient treatment with apixaban or warfarin (plus parenteral anticoagulant bridging therapy) following their index encounters	N=35,756 Up to 180 days	Primary: Major bleeding, clinically relevant non-major bleeding and recurrent VTE Secondary: Not reported	Primary: Incidence proportions for apixaban versus warfarin, respectively, were 1.7% versus 2.3% for major bleeding, 7.0% versus 9.4% for clinically relevant non-major bleeding and 2.3% versus 2.9% for recurrent VTE. In shared frailty models, risks of major bleeding (HR, 0.75; 95% CI, 0.64 to 0.87), clinically relevant non-major bleeding (HR, 0.77; 95% CI, 0.71 to 0.83) and recurrent VTE (HR, 0.80; 95% CI, 0.70 to 0.91) were lower for apixaban versus warfarin. Secondary: Not reported
Male et al.[84] (2020) EINSTEIN-Jr Rivaroxaban bodyweight-adjusted (tablets or suspension) in a 20 mg equivalent dose QD or BID vs	MC, OL, RCT Patients birth to 17 years of age with objectively confirmed VTE for which heparin treatment was initiated	N=500 3 months	Primary: Symptomatic recurrent VTE Secondary: Composite of overt major and clinically relevant non-major bleeding, composite of recurrent VTE	Primary: After a median follow-up of 91 days in children who had a study treatment period of three months (N=463) and 31 days in children who had a study treatment period of one month (N=37), symptomatic recurrent VTE occurred in four (1%) of the 335 children in the rivaroxaban group and in five (3%) of the 165 children in the standard anticoagulation group (HR, 0.40; 95% CI, 0.11 to 1.41) and an absolute difference in risk of 1.8 percentage points (95% CI, -0.6 to 6.0). Fatal VTE did not occur. Secondary: Clinically relevant bleeding was observed in ten (3%) of the 329 rivaroxaban recipients (all were non-major) and in three (2%) of the 162 standard

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
standard anticoagulation therapy (heparin or switched to vitamin K antagonist)			and deterioration on repeat imaging	anticoagulation recipients (two major and one non-major [HR, 1.58; 95% CI, 0.51 to 6.27]), an absolute difference in risk of 1.2 percentage points (95% CI, -2.8 to 4.0). The major bleeding events presented as an intracranial and pulmonary bleeding. The composite of recurrent VTE or major bleeding occurred in four (1%) of 335 children in the rivaroxaban group and seven (4%) of 165 children in the standard anticoagulation group (HR, 0.30; 95% CI, 0.08 to 0.93). Repeat imaging showed improved clot resolution with rivaroxaban as compared with standard anticoagulation (test for ordered categories, P=0.012). Complete resolution of the index thrombosis occurred in 128 children (38%) in the rivaroxaban group as compared with 43 children (26%) in the standard anticoagulation group (OR, 1.70; 95% CI, 1.11 to 2.58; P=0.012). Only one child in each treatment group had an asymptomatic deterioration.
Treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and of PE				
Fuji et al.[85] (2014) STARS E-3 Edoxaban 30 mg QD vs enoxaparin 2000 IU SC BID	DB, DD, RCT Men and women aged 20 to 84 years who were scheduled to undergo unilateral TKA, excluding revision arthroplasty	N=716 11 to 14 days	Primary: Composite of symptomatic PE and symptomatic and asymptomatic DVT, bleeding, adverse events Secondary: Proportion of patients with one or more thromboembolic events	Primary: The composite primary efficacy occurred in 22 of 299 (7.4%) patients receiving edoxaban and 41 of 295 (13.9%) patients receiving enoxaparin (relative risk reduction, 46.8%), indicating non-inferiority (P<0.001) and superiority (P=0.010) of edoxaban relative to enoxaparin. The incidence of major bleeding events was 1.1% (4/354) compared with 0.3% (1/349) in the edoxaban and enoxaparin treatment groups, respectively (P=0.373). The incidence of all bleeding events (major bleeding, clinically relevant non-major bleeding, and minor bleeding) was 22.3% (79/354) in the edoxaban group and 18.9% (66/349) in the enoxaparin group (P=0.265). The incidence of adverse events was slightly lower in the edoxaban group (66.9% [237/354]) compared with the enoxaparin group (73.4% [256/349]), and no difference was observed in the incidence of serious adverse events between the treatment groups. Secondary: The incidence of symptomatic DVT, proximal DVT, symptomatic PE, or VTE-related mortality, were 1.3% (4/299) in the edoxaban group and 0.7% (2/295) in the enoxaparin group (P=NS).
Buller et al.[86]	DB, NI, RCT	N=8,292	Primary	Primary Efficacy:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2013) HOKUSAI-VTE Edoxaban 60 mg QD vs edoxaban 30 mg QD (patients with CrCl 30 to 50 mL/min, a body weight < 60 kg, or receiving a concomitant P-glycoprotein inhibitor such as verapamil or quinidine) vs warfarin (adjusted dose to maintain an INR between 2.0 and 3.0)	Patients ≥ 18 years of age with objectively diagnosed, acute, symptomatic DVT or PE initially started on heparin therapy with either LMWH or unfractionated heparin	12 months	Efficacy: Incidence of adjudicated symptomatic recurrent venous thromboembolism, defined as a composite of DVT or nonfatal or fatal PE Primary Safety: Incidence of adjudicated clinically relevant bleeding, defined as a composite of major or clinically relevant non major bleeding Secondary: Not reported	A recurrence of venous thromboembolism during the overall study period occurred in 130 of 4118 patients (3.2%) in the edoxaban group and in 146 of 4122 patients (3.5%) in the warfarin group (HR, 0.89; 95% CI, 0.70 to 1.13; P<0.001). Primary Safety: Clinically relevant bleeding (major or non-major) occurred in 349 of 4118 patients (8.5%) in the edoxaban group as compared with 423 of 4122 patients (10.3%) in the warfarin group (HR, 0.81; 95% CI, 0.71 to 0.94; P=0.004). Secondary: Not reported
Weitz et al.[87] (2017) EINSTEIN CHOICE Rivaroxaban 10 mg QD vs rivaroxaban 20 mg	DB, RCT Patients ≥18 years of age with objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism; who had	N=3,365 1 year (after 6 to 12 months of therapy)	Primary: Composite of symptomatic, recurrent fatal or nonfatal venous thromboembolism and unexplained death for which pulmonary embolism could	Primary: A primary efficacy outcome event occurred in 17 of 1107 patients (1.5%) who were receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) who were receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) who were receiving aspirin. Fatal venous thromboembolism occurred in two patients (0.2%) who were receiving 20 mg of rivaroxaban, in no patients who were receiving 10 mg of rivaroxaban, and in two patients (0.2%) who were receiving aspirin. Both rivaroxaban doses were superior to aspirin with respect to the primary efficacy outcome (HR for 20 mg of rivaroxaban vs aspirin, 0.34; 95% CI, 0.20 to 0.59; HR for 10 mg of rivaroxaban vs aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). The HR for the comparison

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs aspirin 100 mg QD	been treated for 6 to 12 months with an anticoagulant agent, including a vitamin K antagonist or a direct oral anticoagulant agent such as dabigatran, rivaroxaban, apixaban, or edoxaban; and had not interrupted therapy for more than 7 days before randomization		not be ruled out; major bleeding Secondary: MI, ischemic stroke, systemic embolism, venous thrombosis in locations other than the deep veins of the lower limbs, and death from any cause	between the 20-mg and 10-mg rivaroxaban regimens was 1.34 (95% CI, 0.65 to 2.75; P=0.42). Similar results were found for the other efficacy outcomes. Major bleeding occurred in six patients (0.5%) in the 20-mg rivaroxaban group and in five patients (0.4%) in the 10-mg rivaroxaban group, as compared with three patients (0.3%) in the aspirin group. Secondary: Myocardial infarction, stroke, or systemic embolism occurred in three patients (0.3%) in the 20-mg rivaroxaban group, in five patients (0.4%) in the 10-mg rivaroxaban group, and in seven patients (0.6%) in the aspirin group. The rates of death from any cause were 0.7% and 0.2% in the 20-mg and 10-mg rivaroxaban groups, respectively, as compared with 0.6% in the aspirin group. Rates of adverse events were similar in the three study groups.
EINSTEIN Investigators[88] (2010) EINSTEIN-DVT and EINSTEIN-EXT Rivaroxaban 15 mg BID for three weeks followed by 20 mg QD vs enoxaparin 1 mg/kg SC BID plus warfarin or acenocoumarol started within 48 hours of randomization and	AC, MC, OL, NI, RCT (EINSTEIN-DVT) DB, MC, PC, RCT (EINSTEIN-EXT) Patients with acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE; for enrollment into the extension phase, patients had objectively confirmed symptomatic DVT or PE and had been	N=3,449 Up to 12 months (both studies)	Primary: Symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE), clinically relevant bleeding (EINSTEIN-DVT) or major bleeding (EINSTEIN-EXT) Secondary: All-cause mortality, vascular events (ACS, ischemic stroke, TIA, or systemic	Primary: EINSTEIN-DVT A symptomatic, recurrent VTE occurred in 2.1% of patients treated with rivaroxaban and 3.0% of patients receiving standard therapy with enoxaparin (HR, 0.68; 95% CI, 0.44 to 1.04; P<0.001 for non inferiority, and P=0.08 for superiority). There was no statistically significant difference in the occurrence of clinically relevant (first major or clinically relevant nonmajor) bleeding between patients receiving rivaroxaban or standard therapy with enoxaparin (8.1% for both, HR, 0.97; 95% CI, 0.76 to 1.22; P=0.77). EINSTEIN-EXT Symptomatic, recurrent VTE occurred in eight patients in the rivaroxaban group and 42 patients in the placebo group (1.3 vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; P<0.001). Major bleeding occurred in four patients in the rivaroxaban group and zero patients in the placebo group (P=0.11). Secondary: EINSTEIN-DVT All-cause mortality was similar between patients treated with rivaroxaban or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adjusted to maintain an INR of 2.0 to 3.0 Enoxaparin was discontinued when the INR was ≥2.0 for two consecutive days and the patient had received at least five days of enoxaparin treatment. In the EINSTEIN-EXT trial, patients were randomized to receive rivaroxaban 20 mg QD or placebo for six to 12 months.	treated for six to 12 months with rivaroxaban or acenocoumarol or warfarin (in the EINSTEIN studies or from routine care)		embolism), and net clinical benefit (composite of the primary efficacy outcome or major bleeding)	standard therapy with enoxaparin (2.2 vs 2.9%, respectively; HR, 0.67; 95% CI, 0.44 to 1.02; P=0.06). There was no statistically significant difference in vascular events between patients receiving rivaroxaban or standard therapy with enoxaparin (0.7 vs 0.8%, respectively; HR, 0.79; 95% CI, 0.36 to 1.71; P=0.55). There was a significantly greater net clinical benefit with rivaroxaban compared to standard therapy with enoxaparin (2.9 vs 4.2%; HR, 0.67; 95% CI, 0.47 to 0.95; P=0.03). EINSTEIN-EXT There was one death in the rivaroxaban treatment group and two deaths in the placebo group during follow up (P value not reported). There was no statistically significant difference in vascular events between patients receiving treatment with rivaroxaban or placebo (0.5 vs 0.7%, respectively; HR, 0.74; 95% CI, 0.17 to 3.3; P=0.69). There was a significantly greater net clinical benefit in patients who received rivaroxaban compared to placebo (2.0 vs 7.1%; HR, 0.28; 95% CI, 0.15 to 0.53; P<0.001).
EINSTEIN PE Investigators[89] (2012) EINSTEIN-PE Rivaroxaban 15 mg BID for three weeks followed by 20 mg QD vs enoxaparin 1 mg/kg SC BID plus warfarin or	AC, MC, NI, OL, RCT Patients with an acute, symptomatic PE with objective confirmation, with or without symptomatic DVT Patients were ineligible if they had received a therapeutic dose of LMWH,	N=4,832 Up to 12 months	Primary: Symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE) and clinically relevant bleeding Secondary: Major bleeding, death from any cause, vascular events (ACS, ischemic	Primary: Symptomatic, recurrent VTE occurred in 50 patients (2.1%) receiving rivaroxaban and 44 patients (1.8%) receiving standard therapy with enoxaparin (HR, 1.12; 95% CI, 0.75 to 1.68; P=0.003 for non inferiority and P=0.57 for superiority). Recurrent, nonfatal VTE was suspected in 491 patients in the rivaroxaban group and in 453 patients in the standard therapy group. Major or clinically relevant nonmajor bleeding occurred in 249 patients (10.3%) receiving rivaroxaban and 274 patients (11.4%) receiving standard therapy with enoxaparin (HR, 0.90; 95% CI, 0.76 to 1.07; P=0.23). Secondary: Major bleeding occurred in 26 patients (1.1%) receiving rivaroxaban treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acenocoumarol started within 48 hours of randomization and adjusted to maintain an INR of 2.0 to 3.0 Enoxaparin was discontinued when the INR was ≥2.0 for two consecutive days and the patient had received at least five days of enoxaparin treatment.	fondaparinux, or UFH for more than 48 hours or if they had received more than a single dose of a VKA before randomization.		stroke, TIA, or systemic embolism) and net clinical benefit (composite of the primary efficacy outcome and major bleeding)	compared to 52 patients (2.2%) receiving standard therapy with enoxaparin (HR, 0.49; 95% CI, 0.31 to 0.79, P=0.003). There was no statistically significant difference in death from any cause between patients receiving rivaroxaban or standard therapy (2.4 vs 2.1%, respectively, HR, 1.13; 95% CI, 0.77 to 1.65; P=0.53). Fifteen patients in the rivaroxaban group and 21 patients in the standard therapy group experienced an acute coronary event (P value not reported). A cerebrovascular event was reported in 12 and 13 patients receiving rivaroxaban or standard therapy with enoxaparin, respectively (P value not reported). A systemic embolism occurred in five patients receiving rivaroxaban and three patients receiving standard therapy (P value not reported). A net clinical benefit was reported in 83 patients (3.4%) in the rivaroxaban group and 96 patients (4.0%) in the standard therapy group (HR, 0.85; 95% CI, 0.63 to 1.14; P=0.28).
Thromboprophylaxis in Pediatric Patients after Fontan Procedure				
McCrindle et al.[90] (2021) UNIVERSE Rivaroxaban (suspension) body weight adjusted dosing regimen matching exposure range of 10 mg total daily dose, BID vs acetylsalicylic acid (ASA) 5 mg/kg QD	MC, OL, RCT Patients between 2 and 8 years of age with single-ventricle congenital heart disease and had completed an initial Fontan procedure within 4 months before enrollment	N=100 12 months	Primary: Any thrombotic event or the occurrence of a clinical event known to be strongly associated with thrombus and major bleeding events Secondary: Clinically relevant nonmajor bleeding and trivial bleeding	Primary: In the rivaroxaban group, one patient (2%) was reported with pulmonary embolism on day 84 of study treatment. In the ASA group, three patients (9%) were reported with thrombotic events (two patients [6%] with venous thrombotic events reported on day 177 and day 179 of treatment; and one patient (3%) who had an ischemic stroke on day 122 of treatment). There was one patient with a major bleeding event adjudicated in the rivaroxaban group (2%). There were no patients with major bleeding events reported in the ASA group. Secondary: The proportion of patients with clinically relevant nonmajor bleeding events was less in the rivaroxaban (4 [6%]) than in the ASA group (3 [9%]). In the rivaroxaban group, the bleeding events occurred in the lower gastrointestinal tract (2 [3%]), gingival tissue (1 [2%]), and the skin (1 [2%]). In the ASA group, these events occurred in the lower gastrointestinal tract (1 [3%]), the skin (1 [3%]), hematoma (1 [3%]), and subconjunctival (1 [3%]). The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			events	proportion of patients with trivial bleeding was similar in the rivaroxaban and the ASA groups (21 [33%] versus 12 [35%], respectively). The proportion of patients with any bleeding events was similar in the rivaroxaban group than in the ASA group (36% versus 41%)
Safety				
Uchino et al.[97] (2012) Dabigatran vs control (warfarin, enoxaparin, or placebo)	MA (7 RCTs; 2 trials of stroke prophylaxis in AF, 1 trial in acute VTE, 1 in ACS, and 3 of short term prophylaxis in DVT) Patient population not specified	N=30,514 Duration not specified	Primary: Acute coronary events (MI or ACS) Secondary: Overall mortality	Primary: Dabigatran was significantly associated with a higher risk of MI or ACS compared to control (237/20,000 [1.19%] vs 83/10,514 [0.79%]; OR, 1.33; 95% CI, 1.03 to 1.71; P=0.03). The risk of MI or ACS was similar when using revised RE-LY trial results (OR, 1.27; 95% CI, 1.00 to 1.61; P=0.05) or after exclusion of short term trials (OR, 1.33; 95% CI, 1.03 to 1.72; P=0.03). No relationship between the baseline risk of acute coronary events and the OR for acute coronary events associated with dabigatran use (P=0.61). Secondary: Six trials reported on overall mortality. Dabigatran was significantly associated with lower mortality compared to control (945/19,555 [4.83%] vs 524/10,444 [5.02%]; OR, 0.89; 95% CI, 0.80 to 0.99; P=0.04).

*Agent not available in the United States.
†Not Food and Drug Administration approved for this indication.
Drug regimen abbreviations: BID=twice daily, SC=subcutaneous, QD=once daily
Study abbreviations: AC=active control, ARD=absolute risk difference, ARR=absolute risk reduction, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, ITT=intention-to-treat, MA=meta analysis, MC=multicenter, NI=non inferiority, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PP=per-protocol, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: ACS=acute coronary syndrome, AF=atrial fibrillation, ALT=alanine transaminase, CABG=coronary artery bypass graft surgery, CAD=coronary artery disease, cTTR=center's mean time in therapeutic range, DTI=direct thrombin inhibitor, DVT=deep vein thrombosis, ECG=electrocardiogram, FDA=Food and Drug Administration, GUSTO= Global Utilization Of Streptokinase and Tpa For Occluded Arteries, HIT=heparin induced thrombocytopenia, INR=International Normalized Ratio, LMWH=low molecular weight heparin, LVEF=left ventricular ejection fraction, MI=myocardial infarction, NSAID=nonsteroidal anti-inflammatory drug, NYHA=New York Heart Association, PE=pulmonary embolism, TIA=transient ischemic attack, TIMI=Thrombolysis in Myocardial Infarction, TKA=total knee arthroplasty, TTR=time in therapeutic range, UFH=unfractionated heparin, VKA=vitamin k antagonist, VTE=venous thromboembolism

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 13. Relative Cost of the Oral Anticoagulants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Apixaban	tablet	Eliquis®	$$$$$	N/A
Dabigatran	capsule, pellet pack	Pradaxa®*	$$$$	$$$$
Edoxaban	tablet	Savaysa®	$$$$$	N/A
Rivaroxaban	suspension, tablet	Xarelto®	$$$$$	N/A
Warfarin	tablet	N/A	$$$	$

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

X. Conclusions

The oral anticoagulants include apixaban, dabigatran etexilate mesylate, edoxaban, rivaroxaban, and warfarin. Warfarin has various indications, including prophylaxis and/or treatment of pulmonary embolism (PE); prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation (AF) and/or cardiac valve replacement prophylaxis and/or treatment of venous thrombosis and its extension; and to reduce the risk of death, recurrent myocardial infarction (MI) and thromboembolic events such as stroke or systemic embolization after MI.[5] Warfarin has been the principle oral anticoagulant for the past 60 years in high-risk AF patients.[6] Apixaban, edoxaban, and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor (DTI). All are non-vitamin K oral anticoagulants (NOACs) and are approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF and for treatment

and/or reduction in the risk of recurrence of deep vein thrombosis (DVT) and PE in patients who have previously been treated.[1-4] These agents also have a variety of specific additional cardiovascular indications. Rivaroxaban received expanded indication for two pediatric indications including for treatment of venous thromboembolism and reduction in the risk of recurrent venous thromboembolism in pediatric patients birth to 18 years of age and for thromboprophylaxis in pediatric patients two years of age and older with congenital heart disease after the Fontan procedure.[4] Dabigatran has gained indications in pediatric patients as young as three months of age with approval of the oral pellet dosage form.[2]

In 2014, the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society released an updated guideline on the management of AF. The guidelines state that antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding, and the patient's values and preferences. Dietary limitations and the need for repeated International Normalized Ratio (INR) testing are eliminated with the new agents. If patients are stable, their condition is easily controlled, and they are satisfied with warfarin therapy, it is not necessary to change to a new agent. Notably, patients with mechanical heart valves or hemodynamically significant mitral stenosis were excluded from all three major trials (RE-LY[34], ROCKET AF[48], and ARISTOTLE[28]); therefore, these patients should be managed with warfarin.[12] A 2019 focused update of this guideline recommends NOACs over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).[13] The American College of Chest Physicians released Antithrombotic Therapy for VTE Disease in 2016 which state that NOACs are suggested over warfarin for initial and long-term treatment of VTE in patients without cancer.[9] No NOAC is preferred over another.[9] Since publication of the 9th edition, new studies show that NOACs are as effective as VKA therapy with reduced risk of bleeding and increased convenience for patients and health-care providers.[6] A Science Advisory by the American Heart Association and American Stroke Association states that apixaban, dabigatran etexilate mesylate, and rivaroxaban are recommended as alternatives to warfarin in patients with AF who have at least one additional risk factor for stroke.[11] The American Heart Association/American Stroke Association Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack from 2021 offer recommendations consistent with other published guidelines.[23]

In a large head-to-head trial comparing apixaban to warfarin, less major bleeding and intracranial bleeding was found in the apixaban group, and a similar incidence of gastrointestinal bleeding was found between the groups. Notably, apixaban reduced stroke or systemic embolism and death from any cause compared to warfarin.[28] In two studies apixaban was shown to reduce the risk of DVT and PE after hip or knee surgery, with similar bleeding rates compared to once daily enoxaparin.[81,82]

Dabigatran etexilate mesylate 110 mg twice-daily demonstrated similar efficacy for reducing the risk of stroke and systemic embolism when compared to warfarin. In this trial, the incidence of major bleeding was reduced with dabigatran etexilate mesylate treatment. In general, evidence suggests that the two agents are comparable in terms of overall bleeding, with more intracranial bleeding being associated with warfarin and more gastrointestinal bleeding being associated with dabigatran etexilate mesylate.[34] Studies have also shown that dabigatran etexilate mesylate is more effective than placebo and similarly effective to warfarin for the short- and long-term therapy after VTE to prevent recurrent VTE.[77-79]

Rivaroxaban was compared to warfarin in a large, double-blind trial including over 14,000 patients at risk for stroke. Rivaroxaban performed similarly to warfarin in regard to the primary endpoint, a composite of stroke or systemic embolism. The incidence of major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin was similar. The rate of intracranial bleeding was significantly lower with rivaroxaban compared to warfarin, but major bleeding from a gastrointestinal site was more common with rivaroxaban.[48] For the prophylaxis of DVT, rivaroxaban was evaluated in trials compared to enoxaparin, a low molecular weight heparin agent (LMWH), for use as thromboprophylaxis in patients undergoing hip and knee replacement surgeries. In all four trials, rivaroxaban significantly reduced the risk of the primary composite endpoint of any DVT, nonfatal PE, or death from any cause compared to enoxaparin. In addition, there were similar rates of major bleeding and hemorrhagic wound complications between rivaroxaban and enoxaparin. These trials evaluated both short (10 to 14 days) and extended (31 to 30 days) thromboprophylaxis with rivaroxaban.[65-67] In patients with an acute, symptomatic, proximal DVT without symptomatic PE, and acute, symptomatic PE with or without symptomatic DVT, treatment with rivaroxaban was associated with a reduction in symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE) compared to standard therapy, without an increase in bleeding events.[88,89]

As with the other NOACs, edoxaban is predominately cleared by the kidneys. Recommendations per the package insert are to decrease the dose if CrCl is < 50 mL/min and to avoid use altogether in AF patients with normal renal function (CrCl is > 95 mL/min).[3] For the treatment of nonvalvular AF, the ENGAGE AF-TIMI 48 study demonstrated that high dose edoxaban (60 mg or 30 mg dose adjusted) was noninferior to adjusted dose warfarin for the reduction of the primary composite endpoint of stroke (ischemic or hemorrhagic) or systemic embolic event (P<0.001 for noninferiority). The rate of ischemic stroke was similar with high-dose edoxaban and warfarin but was higher with the low-dose edoxaban regimen.[44] Results from the HOKUSAI-VTE study demonstrated noninferiority of edoxaban to adjusted dose warfarin for the reduction of recurrent, symptomatic DVT and PE in patients treated up to 12 months.[86]

The evidence demonstrating the efficacy of warfarin for FDA-approved indications, including reducing the risk of stroke and systemic embolism in patients with AF, is well established, and warfarin has been considered the standard of care in high-risk patients with AF.[12] Warfarin therapy is associated with several challenges including a slow onset and offset of action, significant and unpredictable inter-individual variability in pharmacologic response, a narrow therapeutic window necessitating frequent monitoring and numerous food and drug interactions. Moreover, maintenance of a therapeutic level of anticoagulation may be difficult for some patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.[6,12] In comparison to warfarin, treatment with apixaban, edoxaban, dabigatran etexilate mesylate, or rivaroxaban does not require routine monitoring, but clinicians may find it difficult to objectively assess a patient's adherence to therapy and to verify if a fixed-dose regimen can be universally applied to all patients. Additionally, compliance with these new oral anticoagulants is critical. Missing even one dose could result in a period without protection from thromboembolism; As a result, the FDA issued black box warnings that discontinuation of these new agents can increase the risk of thromboembolism and that coverage with another anticoagulant may be needed.[1-4,12] Warfarin does not require a dosage adjustment in patients with renal impairment, while a lower dose of apixaban, dabigatran etexilate mesylate, and rivaroxaban (in AF only) is recommended.[1-5] Moreover, apixaban requires a dosage adjustment when two or more of the following factors are present: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL.[1] Edoxaban also has a boxed warning for reduced efficacy in nonvalvular atrial fibrillation patients with CrCl >95 ml/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL >95 mL/min had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used.[3]

In summary, the NOACs have been shown to be at least as effective as VKA therapy. Guidelines recommend NOACs over warfarin for initial and long-term treatment of VTE in patients without cancer. AF guidelines recommend NOACs over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve). VKA therapy is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves. There is insufficient evidence to conclude that one NOAC is safer or more efficacious than another for its approved indications.

NOACs may offer significant clinical advantages in VTE patients, but are comparable to each other. VKA products may offer significant clinical advantages in AF patients with mitral stenosis or mechanical heart valves, but are comparable to each other. In other patient populations with FDA-approved indications for an oral anticoagulant, all brand products within the class reviewed 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.

XI. Recommendations

No brand oral anticoagulant, with the exception of a non-vitamin K oral anticoagulant (NOAC) agent, 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 or generic apixaban, dabigatran, edoxaban, or rivaroxaban product is selected as a preferred agent.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Platelet-Aggregation Inhibitors
AHFS Class 201218
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I. Overview

The platelet-aggregation inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes, angina, intermittent claudication, myocardial infarction, stroke, and transient ischemic attack.[1-7]

The platelet-aggregation inhibitors exert their pharmacologic effects through several different mechanisms. Clopidogrel is a thienopyridine, which works by blocking the adenosine diphosphate (ADP) receptors found on platelets, leading to a subsequent inhibition of both platelet aggregation and activation.[5] The platelet inhibition effects of thienopyridines are delayed; therefore, a loading dose is typically required with these agents.[1-2] Prasugrel is a third generation thienopyridine ADP receptor antagonist; therefore, it has a similar mechanism of action to that of clopidogrel. Prasugrel has been reported to be the most potent of these agents with a 10 mg dose of prasugrel being approximately 2.5 to 2.7 times more potent than a 75 mg dose of clopidogrel in inhibiting platelet aggregation and thrombus formation.[8] This reported greater efficacy in platelet inhibition is due to the difference in cytochrome activation between the agents. Clopidogrel requires a multi-step cytochrome activation process, whereas prasugrel requires only a single step.[9] Prasugrel has been shown to have more desirable characteristics when compared to clopidogrel with regards to drug-drug interactions and interpatient enzyme variability. Looking more specifically at drug-drug interactions, potent cytochrome P450 (CYP) 3A4 inhibitors have been shown to affect clopidogrel; however, no effect has been seen with prasugrel, suggesting that no dosage adjustments are necessary when faced with this type of interaction. Regarding polymorphism, studies have shown that clinical outcomes with prasugrel are not affected by patient genetic variations of the CYP2C9 and 2C19 isoenzymes, which have been reported with clopidogrel.[10] Ticagrelor also works in a similar manner to the other thienopyridine platelet inhibitors. Specifically, ticagrelor is a cyclopentyltriazolopyrimidine, and the agent and its equipotent active metabolite reversibly bind to the $P2Y_{12}$ receptor located on the surface of platelets, preventing platelet signal transduction and activation.[2,3] In contrast to ticagrelor, the other available thienopyridines work via the irreversible binding to the $P2Y_{12}$ receptor. In addition, these agents are all prodrugs, while ticagrelor is not. Therefore, ticagrelor does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other platelet inhibitors.[3,5,7] When compared to clopidogrel, ticagrelor resulted in lower platelet receptor expression and a greater extent of inhibition of platelet aggregation, suggesting increased potency at the $P2Y_{12}$ receptor.[11] Cilostazol inhibits phosphodiesterase activity and suppresses the degradation of cyclic-3',5'-adenosine monophosphate in platelets and blood vessels.[7]

Vorapaxar, is a reversible antagonist of protease-activated receptor 1 (PAR-1). Blocking PAR-1 results in potent inhibition of thrombin-induced platelet aggregation.[12] Due to vorapaxar's long half-life, it acts as an irreversible inhibitor. Unlike other platelet inhibitors, vorapaxar does not inhibit platelet aggregation induced by ADP, collagen, or a thromboxane mimetic.[2,6]

The platelet-aggregation inhibitors that are included in this review are listed in Table 1. Dipyridamole, vericiguat, and aspirin-dipyridamole are now classified in the vasodilating agents, miscellaneous AHFS class. Currently, cilostazol, clopidogrel, and prasugrel are available generically. This review encompasses all dosage forms and strengths. This class was last reviewed in February 2022.

Table 1. Platelet-Aggregation Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cilostazol	tablet	N/A	cilostazol
Clopidogrel	tablet	Plavix®*	clopidogrel
Prasugrel	tablet	Effient®*	prasugrel
Ticagrelor	tablet	Brilinta®	Brilinta®
Vorapaxar	tablet	Zontivity®	none

*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 treatment guidelines that incorporate the use of the platelet-aggregation inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Platelet-Aggregation Inhibitors

Clinical Guideline	Recommendations
American College of Chest Physicians: **Antithrombotic Therapy and Prevention of Thrombosis, 9th edition (2012)**[13]	Management of anticoagulant therapy • For outpatients, vitamin K antagonist (VKA) therapy with warfarin 10 mg/day for the first two days, followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose is suggested. • Routine use of pharmacogenetic testing for guiding doses of VKA therapy is not recommended. • For acute venous thromboembolism (VTE), it is suggested that VKA therapy be started on day one or two of low molecular weight heparin (LMWH) or low dose unfractionated heparin (UFH) therapy rather than waiting for several days to start. • For VKA therapy with stable INRs, INR testing frequency of up to 12 weeks is suggested rather than every four weeks. • For patients receiving previously stable VKA therapy who present with a single out-of-range INR ≤0.5 below or above therapeutic, it is suggested to continue the current dose and test the INR within one to two weeks. • For patients receiving stable VKA therapy presenting with a single subtherapeutic INR value, routine administering of bridging heparin is not recommended. • Routine use of vitamin K supplementation is suggested against with VKA therapy. • For patients receiving VKA therapy who are motivated and can demonstrate competency in self-management strategies, it is suggested that patient self-management be utilized rather than usual outpatient INR monitoring. • For maintenance VKA dosing, it is suggested that validated decision support tools be utilized rather than no decision support. • Concomitant use of nonsteroidal anti-inflammatory drugs and certain antibiotics should be avoided in patients receiving VKA therapy. • Concomitant use of platelet inhibitors should be avoided in patients receiving VKA therapy, except in situations where benefit is known or is highly likely to be greater than harm from bleeding. • With VKA therapy, a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended rather than a lower (<2.0) or higher (range, 3.0 to 5.0) range. • In patients with antiphospholipid syndrome with previous arterial or VTE, VKA therapy should be titrated to a moderate intensity INR (range, 2.0 to 3.0) rather than higher intensity (range, 3.0 to 4.5). • For discontinuations of VKA therapy, it is suggested that discontinuation be done abruptly rather than gradual tapering of the dose. • For initiation of intravenous (IV) UFH, the initial bolus and rate of continuous infusion should be weight adjusted or fixed-dose rather than alternative regimens. • In outpatients with VTE receiving subcutaneous (SC) UFH, dosing should be weight-based without monitoring rather than fixed or weight-adjusted dosing with monitoring. • A reduction in therapeutic LMWH dose is suggested in patients with severe

Clinical Guideline	Recommendations
	renal insufficiency rather than using standard doses. • In patients with VTE and body weight >100 kg, the treatment dose of fondaparinux should be increased from 7.5 to 10 mg/day SC. • For INRs between 4.5 and 10.0 with VKA therapy and no evidence of bleeding, routine use of vitamin K is not recommended. • For INRs >10.0 with VKA therapy and no evidence of bleeding, it is suggested that oral vitamin K be administered. • In patients initiating VKA therapy, routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy is not recommended. • For VKA-associated major bleeding, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate is suggested over plasma. Additional use of vitamin K 5 to 10 mg administered by slow IV injection is recommended rather than reversal with coagulation factors alone. <u>Prevention of VTE in nonsurgical patients</u> • Acutely ill hospitalized medical patients at increased risk of thrombosis: anticoagulant thromboprophylaxis with LMWH, low dose UFH (two or three times daily), or fondaparinux is recommended. Choice should be based on patient preference, compliance, and ease of administration, as well as on local factors affecting acquisition costs. • Acutely ill hospitalized patients at low risk of thrombosis: pharmacologic or mechanical prophylaxis is not recommended. • Acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding: anticoagulant thromboprophylaxis is not recommended. • Acutely ill hospitalized medical patients at increased risk for thrombosis who are bleeding or at high risk of major bleeding: optimal use of mechanical thromboprophylaxis is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, it is suggested that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis. • Acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis: extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay is suggested against. • Critically ill patients: routine ultrasound screening for deep vein thrombosis (DVT) is suggested against. • Critically ill patients: use of LMWH or low dose UFH thromboprophylaxis is suggested over no prophylaxis. • Critically ill patients who are bleeding or are at high risk for major bleeding: use of mechanical thromboprophylaxis until the bleeding risk decreases is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, pharmacologic thromboprophylaxis is suggested to be substituted for mechanical thromboprophylaxis. • Outpatients with cancer who have no additional risk factors for VTE: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is not recommended. • Outpatients with solid tumors who have additional risk factors for VTE with low risk of bleeding: prophylaxis with LMWH or low dose UFH is suggested over no prophylaxis. • Outpatients with cancer and indwelling central venous catheters: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is suggested against. • Chronically immobilized patients residing at home or at a nursing home: routine thromboprophylaxis is suggested against. • Long distance travelers at increased risk of VTE: frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible is suggested.

Clinical Guideline	Recommendations
	• Long distance travelers at increased risk of VTE: use of properly fitted, below-knee graduated compression stockings during travel is suggested. For all other long distance travelers, use of graduated compression stockings is suggested against. • Long distance travelers: use of aspirin or anticoagulants to prevent VTE is suggested against. • Patients with asymptomatic thrombophilia: long term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE is not recommended. <u>Prevention of VTE in nonorthopedic surgical patients</u> • General and abdominal-pelvic surgery patients at very low risk for VTE: no specific pharmacologic or mechanical prophylaxis is recommended for use other than early ambulation. • General and abdominal-pelvic surgery patients at low risk for VTE: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are not at high risk major bleeding complications: LMWH, low dose UFH, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at high risk for VTE who are not at high risk for major bleeding complications: LMWH or low dose UFH is recommended over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • High-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications: extended duration (four weeks) of LMWH prophylaxis is recommended over limited duration prophylaxis. • High-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • General and abdominal-pelvic surgery patients at high risk for VTE in whom both LMWH and UFH are contraindicated or unavailable and who are not at high risk for major bleeding complications: low dose aspirin, fondaparinux, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients: it is suggested that an inferior vena cava filter not be used for primary VTE prevention. • General and abdominal-pelvic surgery patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. • Cardiac surgery patients with an uncomplicated postoperative course: mechanical prophylaxis is suggested over either no prophylaxis or pharmacologic prophylaxis. • Cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications: adding pharmacologic prophylaxis with low dose UFH or LMWH to mechanical prophylaxis is suggested. • Thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding: low dose UFH or LWMH is suggested over no prophylaxis. It is suggested that mechanical prophylaxis be added to

Clinical Guideline	Recommendations
	pharmacologic prophylaxis. • Thoracic surgery patients who are at high risk for major bleeding: mechanical prophylaxis over no prophylaxis is suggested until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • Craniotomy patients: mechanical prophylaxis is suggested over no prophylaxis or pharmacologic prophylaxis. • Craniotomy patients at very high risk for VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Patients undergoing spinal surgery: mechanical prophylaxis is suggested over no prophylaxis, UFH, or LMWH. • Patients undergoing spinal surgery at high risk of VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Major trauma patients: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Major trauma patients at high risk for VTE: it is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis when not contraindicated by lower extremity injury. • Major trauma patients in whom LMWH and low dose UFH are contraindicated: mechanical prophylaxis is suggested over no prophylaxis when not contraindicated by lower extremity injury. It is suggested that either LMWH or low dose UFH be added when the risk of bleeding diminishes or the contraindication to heparin resolves. • Major trauma patients: it is suggested that an interior vena cava filter not be used for primary VTE prevention. • Major trauma patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. <u>Prevention of VTE in orthopedic surgery patients</u> • Total hip arthroplasty or total knee arthroplasty: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, aspirin, or an intermittent pneumatic compression device. • Hip fracture surgery: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, low dose UFH, adjusted-dose VKA, aspirin, or intermittent pneumatic compression device. • Patients undergoing major orthopedic surgery (total hip arthroplasty, total knee arthroplasty, hip fracture surgery) and receiving LMWH as thromboprophylaxis: it is recommended to start either 12 hours or more preoperatively or postoperatively rather than within four hours or less preoperatively or postoperatively. • Total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, or aspirin. • Hip replacement surgery, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, low dose UFH, adjusted-dose VKA, or aspirin. • Major orthopedic surgery: it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only

Clinical Guideline	Recommendations
	10 to 14 days. • Major orthopedic surgery: it is suggested to use dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the hospital stay. • Major orthopedic surgery in patients at an increased risk of bleeding: intermittent pneumatic compression device or no prophylaxis is suggested over pharmacologic prophylaxis. • Major orthopedic surgery in patients who decline or are uncooperative with injections or intermittent pneumatic compression device: apixaban or dabigatran etexilate mesylate (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran etexilate mesylate are unavailable) is recommended over alternative forms of prophylaxis. • Major orthopedic surgery in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical prophylaxis: inferior vena cava filter placement for primary prevention of VTE is suggested against over no thromboprophylaxis. • Asymptomatic patients following major orthopedic surgery: Doppler ultrasound screening before hospital discharge is not recommended. • Patients with lower leg injuries requiring leg immobilization: no prophylaxis is suggested rather than pharmacologic thromboprophylaxis. • Knee arthroscopy in patients without a history of prior VTE: no thromboprophylaxis is suggested rather than prophylaxis. <u>Antithrombotic therapy for VTE disease</u> • Acute DVT of the leg or pulmonary embolism (PE) treated with VKA therapy: initial treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) is recommended over no such initial treatment. • High clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment while awaiting the results of diagnostic tests. • Intermediate clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment if the results of diagnostic tests are expected to be delayed for more than four hours. • Low clinical suspicion of acute VTE or PE: it is suggested to not treat with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours. • Acute isolated distal DVT of the leg without severe symptoms or risk factors for extension: serial imaging of the deep veins for two weeks is suggested over initial anticoagulation. • Acute isolated distal DVT of the leg and severe symptoms or risk factors for extension: initial anticoagulation is suggested over serial imaging of the deep veins. • Acute isolated distal DVT of the leg in patients managed with initial anticoagulation: using the same approach as for patients with acute proximal DVT is recommended. • Acute isolated distal DVT of the leg who are managed with serial imaging: no anticoagulation if the thrombus does not extend is recommended; anticoagulation is suggested if the thrombus extends but remains confined to the distal veins; and anticoagulation is recommended if the thrombus extends into the proximal veins. • Acute DVT of the leg or PE: early initiation of VKA therapy is recommended over delayed initiation, and continuation of parenteral anticoagulation for a minimum on five days and until the INR is 2.0 or above for at least 24 hours. • Acute DVT of the leg or PE: LMWH or fondaparinux is suggested over IV or SC UFH.

Clinical Guideline	Recommendations
	• Patients with acute DVT of the leg or PE receiving LMWH: once daily LMWH administration is suggested over twice daily administration. • Acute DVT of the leg and home circumstances are adequate: initial treatment at home is recommended over treatment in hospital. • Low risk PE and home circumstances are adequate: early discharge is suggested over standard discharge. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over catheter-directed thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over systemic thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over venous thrombectomy. • Acute DVT of the leg in patients who undergo thrombosis removal: the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal is recommended. • Acute DVT of the leg: use of an inferior vena cava filter in addition to anticoagulants is not recommended. • Acute proximal DVT of the leg in patients with contraindication to anticoagulation: use of an inferior vena cava filter is recommended. • Acute proximal DVT of the leg in patients with an inferior vena cava filter inserted as an alternative to anticoagulation: a conventional course of anticoagulant therapy is suggested if the risk of bleeding resolves. • Acute DVT of the leg: early ambulation is suggested over initial bed rest. • Acute VTE in patients receiving anticoagulant therapy: long term therapy is recommended over stopping anticoagulant therapy after about one week of initial therapy. • Acute symptomatic DVT of the leg: compression stockings are suggested. • Acute PE associated with hypotension in patients who do not have a high bleeding risk: systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension: systemically administered thrombolytic therapy is not recommended. • In selected patients with acute PE not associated with hypotension and with a low bleeding risk who initial clinical presentation or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension: administration of thrombolytic therapy is suggested. • Proximal DVT of the leg or PE provoked by surgery: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment of a longer time limited period, or extended therapy. • Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment for a longer time limited period, extended therapy if there is high bleeding risk. Anticoagulation treatment for three months is suggested over extended therapy if there is a low or moderate bleeding risk. • Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor: treatment with anticoagulation for three months is suggested over treatment for a shorter period, and anticoagulation treatment for three months is recommended over treatment of longer time limited period or extended therapy. • Unprovoked DVT of the leg or PE: treatment with anticoagulation for three months is recommended over treatment of a shorter duration. After three months, patients should be evaluated for the risk-benefit ratio of extended therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients

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	who have a low or moderate bleeding risk: extended anticoagulant therapy is suggested over three months of therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a high bleeding risk: three months of anticoagulant therapy is recommended over extended therapy. • First VTE that is an unprovoked isolated distal DVT of the leg: three months of anticoagulation therapy is suggested over extended therapy in those with a low or moderate bleeding risk, and three months of anticoagulant treatment is recommended in those with a high bleeding risk. • Second unprovoked VTE or PE: extended anticoagulant therapy is recommended over three months of therapy in those who have a low bleeding risk, and extended anticoagulant therapy is suggested in patients with a moderate bleeding risk. • Second unprovoked VTE or PE in patients with a high bleeding risk: three months of anticoagulant therapy is suggested over extended therapy. • DVT of the leg or PE and active cancer: if the risk of bleeding is not high, extended anticoagulation therapy is recommended over three months of therapy, and if there is a high bleeding risk, extended anticoagulant therapy is suggested. • DVT of the leg or PE in patients treated with VKA: a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended over a lower (<2.0) or higher (range, 3.0 to 5.0) range for all treatment durations. • DVT of the leg or PE in patients with no cancer: VKA therapy is suggested over LMWH for long-term therapy. For patients with DVT or PE and no cancer who are not treated with VKA therapy, LMWH is suggested over dabigatran etexilate mesylate or rivaroxaban for long term therapy. • DVT of the leg or PE and cancer: LMWH is suggested over VKA therapy. In patients with DVT of the leg or PE and cancer who are not treated with LMWH, VKA is suggested over dabigatran etexilate mesylate or rivaroxaban for long-term therapy. • DVT of the leg or PE in patients who receive extended therapy: treatment with the same anticoagulant chosen for the first three months is suggested. • Patients incidentally found to have asymptomatic DVT of the leg or PE: treatment with the same anticoagulant is suggested as for comparable patients with symptomatic DVT or PE. • In patients with chronic thromboembolic pulmonary hypertension, extended anticoagulation is recommended over stopping therapy. • Superficial vein thrombosis of the lower limb of at least 5 cm in length: use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation. • Superficial vein thrombosis in patients treated with anticoagulation: fondaparinux 2.5 mg/day is suggested over a prophylactic dose of LMWH. • Upper-extremity DVT that involves the axillary or more proximal veins: acute treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) over no such acute treatment. • Acute upper-extremity DVT that involves the axillary or more proximal veins: LMWH or fondaparinux is suggested over IV or SC UFH, and anticoagulation therapy alone is suggested over thrombolysis. • Upper-extremity DVT in patients undergoing thrombolysis: the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis is recommended. • In most patients with upper-extremity DVT that is associated with a central venous catheter: it is suggested that the catheter not be removed if it is functional and there is an ongoing need for the catheter. • Upper-extremity DVT that involves the axillary or more proximal veins: a

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	minimum duration of anticoagulation of three months is suggested over a shorter duration. • Upper-extremity DVT that is associated with a central venous catheter that is removed: three months of anticoagulation is recommended over a longer duration of therapy in patients with no cancer, and this is suggested in patients with cancer. • Upper-extremity DVT that is associated with a central venous catheter that is not removed: it is recommended that anticoagulation is continued as long as the central venous catheter remains over stopping after three months of treatment in patients with cancer, and this is suggested in patients with no cancer. • Upper-extremity DVT that is not associated with a central venous catheter or with cancer: three months of anticoagulation is recommended over a longer duration of therapy. • Acute symptomatic upper-extremity DVT: use of compression sleeves or venoactive medications is suggested against. • Symptomatic splanchnic vein thrombosis: anticoagulation is recommended over no anticoagulation. • Symptomatic hepatic vein thrombosis: anticoagulation is suggested over no anticoagulation. • In patients with incidentally detected splanchnic vein thrombosis or hepatic vein thrombosis: no anticoagulation is suggested over anticoagulation. <u>Antithrombotic therapy for atrial fibrillation (AF)</u> • Patients with AF, including those with paroxysmal AF, who are at low risk of stroke: no therapy is suggested over antithrombotic therapy. For patients who choose antithrombotic therapy, aspirin is suggested over oral anticoagulation or combination therapy with aspirin and clopidogrel. • Patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke: oral anticoagulation is recommended over no therapy. Oral anticoagulation is suggested over aspirin or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel are suggested over aspirin. • Patients with AF, including those with paroxysmal AF, who are at high risk of stroke: oral anticoagulation is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel is recommended over aspirin. • Patients with AF, including those with paroxysmal AF: for recommendations in favor of oral anticoagulation, dabigatran etexilate mesylate 150 mg twice daily is suggested over adjusted-dose VKA therapy (target INR range, 2.0 to 3.0). • Patients with AF and mitral stenosis: adjusted-dose VKA therapy is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take adjusted-dose VKA therapy, combination therapy with aspirin and clopidogrel is recommended over aspirin alone. • Patients with AF and stable coronary artery disease and who choose oral anticoagulation: adjusted-dose VKA therapy alone is suggested over the combination of adjusted-dose VKA therapy and aspirin. • Patients with AF at high risk of stroke during the first month after placement of a bare-metal stent or the first three to six months after placement of a drug-eluting stent: triple therapy (e.g., VKA therapy, aspirin, and clopidogrel) is suggested over dual antiplatelet therapy (e.g., aspirin and clopidogrel). After

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	this initial period, a VKA plus a single antiplatelet agent is suggested over a VKA alone. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate risk of stroke during the first 12 months after placement of a stent: dual antiplatelet therapy is suggested over triple therapy. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate to high risk of stroke who experience an acute coronary syndrome (ACS) and do not undergo stent placement, for the first 12 months: adjusted-dose VKA therapy plus single antiplatelet therapy is suggested over dual antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at low risk of stroke: dual antiplatelet therapy is suggested over adjusted-dose VKA therapy plus single antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF being managed with a rhythm control strategy: it is suggested that antithrombotic therapy decisions follow the general risk-based recommendations for patients with nonrheumatic AF, regardless of the apparent persistence of normal sinus rhythm. • Patients with atrial flutter: it is suggested that antithrombotic therapy decisions follow the same risk-based recommendations as for AF. <u>Antithrombotic therapy for ischemic stroke</u> • In patients with acute ischemic stroke or transient ischemic attack (TIA), early (within 48 hours) aspirin 160 to 325 mg is recommended over therapeutic parenteral anticoagulation. • In patients with a history of noncardioembolic ischemic stroke or TIA, aspirin (75 to 100 mg daily), clopidogrel (75 mg daily), aspirin-dipyridamole extended-release (ER) (25 mg-200 mg twice daily) or cilostazol (100 mg twice daily) is recommended over oral anticoagulants, the combination of clopidogrel plus aspirin or triflusal. o Clopidogrel or aspirin-dipyridamole ER is recommended over aspirin or cilostazol. • In patients with a history of ischemic stroke or TIA and AF, oral anticoagulation with dabigatran 150 mg twice daily is recommended over VKA therapy. o In patients who are unable to or choose not to take an oral anticoagulant, the combination of aspirin plus clopidogrel is recommended over aspirin alone. <u>Primary and secondary prevention of cardiovascular disease</u> • Patients ≥50 years of age without symptomatic cardiovascular disease: low dose aspirin (75 to 100 mg/day) is suggested over no aspirin therapy. • Patients with established coronary artery disease: long term single antiplatelet therapy with aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended over no antiplatelet therapy, and single antiplatelet therapy is suggested over dual antiplatelet therapy. • Patients in the first year after ACS who have not undergone percutaneous coronary intervention (PCI): dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day or clopidogrel 75 mg/day plus low dose aspirin 75 to 100 mg/day) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin.

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	• Patients in the first year after an ACS who have undergone PCI with stent placement: dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day, clopidogrel 75 mg/day plus low dose aspirin, or prasugrel 10 mg/day plus low dose aspirin) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients with anterior myocardial infarction (MI) and left ventricular thrombus, or at high risk for left ventricular thrombus, who do not undergo stenting: warfarin plus low dose aspirin (75 to 100 mg/day) is recommended over single antiplatelet therapy or dual antiplatelet therapy for the first three months. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, single antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who undergo bare-metal stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for one month is suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the second and third month post-bare-metal stent is suggested over alternative regimens and alternative time frames for warfarin use. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus who undergo drug-eluting stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for up to three to six months is suggested over alternative regimens and alternative durations of warfarin therapy. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective PCI with placement of bare-metal stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for one month is recommended over single antiplatelet therapy. For the subsequent 11 months, dual antiplatelet therapy with combination low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. • Patients who have undergone elective PCI with placement of drug-eluting stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for three to six months is recommended over single antiplatelet therapy. After three to six months, continuation of dual antiplatelet therapy with low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested to be continued until 12 months over antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective bare-metal stent or drug-eluting stent placement: low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is recommended over cilostazol in addition to these drugs. Aspirin 75 to 100 mg/day or clopidogrel 75 mg/day as part of dual antiplatelet therapy is suggested over the use of either drug with cilostazol. Cilostazol 100 mg twice daily as a substitute for either low dose aspirin or clopidogrel as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class is suggested.

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	• Patients with coronary artery disease undergoing elective PCI but no stent placement: for the first month dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients with systolic left ventricular dysfunction without established coronary artery disease and no left ventricular thrombus: it is suggested that antiplatelet therapy and warfarin not be used. • Patients with systolic left ventricular dysfunction without established coronary artery disease with identified acute left thrombus: moderate intensity warfarin for at least three months is suggested. • Patients with systolic left ventricular dysfunction and established coronary artery disease: recommendations are as per the established coronary artery disease recommendations. <u>Antithrombotic therapy in peripheral artery disease (PAD)</u> • In patients with asymptomatic PAD, aspirin 75 to 100 mg daily is recommended. • In patients with symptomatic PAD, long-term therapy with aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) is recommended for secondary prevention of cardiovascular events. Dual antiplatelet therapy or the combination of an antiplatelet agent with moderate-intensity warfarin is not recommended. • Use of cilostazol in addition to aspirin or clopidogrel is recommended in patients with intermittent claudication refractory to exercise therapy and smoking cessation. • Use of prostanoids in addition to aspirin or clopidogrel is recommended in patients with symptomatic PAD and critical leg ischemia who are not candidates for vascular intervention. • In patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, long-term therapy with aspirin or clopidogrel is recommended over dual antiplatelet therapy. • Following peripheral artery bypass graft surgery, long-term therapy with aspirin or clopidogrel is recommended over the combination of antiplatelet agent plus warfarin. Clopidogrel plus aspirin for one year is recommended in patients undergoing below-knee bypass graft surgery with prosthetic grafts. • In patients with asymptomatic carotid stenosis, aspirin 75 to 100 mg daily is recommended. • In patients with symptomatic carotid stenosis, long-term therapy with clopidogrel (75 mg daily) or aspirin/dipyridamole ER (25 mg/200 mg twice daily) is recommended over aspirin (75 to 100 mg daily). <u>Antithrombotic and thrombolytic therapy for valvular disease</u> • Antithrombotic therapy in the first three months after surgery: o In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, aspirin (50 to 100 mg/day) over VKA therapy is suggested in the first three months. o In patients with transcatheter aortic bioprosthetic valves, aspirin (50 to 100 mg/day) plus clopidogrel (75 mg/day) is suggested over VKA therapy and over no antiplatelet therapy in the first three months. o In patients with a bioprosthetic valve in the mitral position, VKA therapy over no VKA therapy for the first three months after valve insertion is suggested. • Long-term antithrombotic therapy for patients with bioprosthetic valves: o In patients with bioprosthetic valves in normal sinus rhythm, aspirin

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	therapy over no aspirin therapy after three months postoperative is suggested. • Early postoperative bridging to intermediate/long-term therapy (postoperative day 0 to 5): o In patients with mechanical heart valves, bridging with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) over intravenous (IV) therapeutic UFH until stable on VKA therapy. • Long-term antithrombotic therapy for patients with mechanical valves: o VKA therapy is recommended over no VKA therapy for long-term management. • Intensity of VKA therapy for patients with mechanical aortic valve prostheses: o VKA therapy at a target of 2.5 over lower targets is suggested. A target of 2.5 is recommended over higher targets. • Intensity of VKA therapy for patients with mechanical mitral valve prostheses: o VKA therapy with a target of 3.0 over lower INR targets is suggested. • Intensity of VKA therapy in patients with double mechanical valve or with additional risk factors: o VKA therapy with a target of 3.0 is suggested over target INR 2.5. • Antiplatelet agent in addition to VKA therapy for patients with mechanical aortic or mitral valve prostheses: o Patients who are at low risk of bleeding, adding over not adding an antiplatelet agent such as low-dose (50 to 100 mg/day) to VKA therapy is suggested. • For patients with mechanical aortic or mitral valves VKA therapy over antiplatelet agents is recommended. • In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, the use of antiplatelet therapy for the first three months is suggested over VKA therapy. • In patients undergoing aortic valve repair, aspirin (50 to 100 mg/day) is suggested over VKA therapy.
American College of Chest Physicians: **Antithrombotic Therapy for VTE Disease (2021)**[14]	<u>Choice of long-term (first three months) and extended (no scheduled stop date) anticoagulant</u> • In patients with proximal deep vein thrombosis (DVT) or pulmonary embolism (PE), long-term (three months) anticoagulant therapy is recommended over no such therapy. • In patients with DVT of the leg or PE and no cancer, as long-term (first three months) anticoagulant therapy, dabigatran, rivaroxaban, apixaban, or edoxaban is recommended over vitamin K antagonist (VKA) therapy. • No non-vitamin K oral anticoagulant is preferred over another. • Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. • In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term anticoagulant therapy, LMWH is recommended over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban. • In patients with DVT of the leg or PE who receive extended therapy, there is no need to change the choice of anticoagulant after the first three months. <u>Duration of anticoagulant therapy</u> • In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension, suggest serial imaging of the deep veins for two weeks over anticoagulation or (ii) with severe symptoms or risk factors for extension. suggest anticoagulation over serial imaging of the deep veins. • In patients with acute isolated distal DVT of the leg who are managed with

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	serial imaging, (i) recommend no anticoagulation if the thrombus does not extend , (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins, and (iii) recommend anticoagulation if the thrombus extends into the proximal veins. • In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE, suggest clinical surveillance over anticoagulation or (ii) high risk for recurrent VTE, suggest anticoagulation over clinical surveillance. • In patients who are incidentally found to have asymptomatic PE, suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE. • In patients with cerebral vein/venous sinus thrombosis, recommend anticoagulation therapy for at least the treatment phase (first three months) over no anticoagulant therapy. • In patients with acute DVT of the leg, suggest anticoagulant therapy alone over interventional (thrombolytic, mechanical, or pharmaco-mechanical) therapy. • In patients with acute PE associated with hypotension (e.g., systolic BP <90 mmHg) who do not have a high bleeding risk, suggest systemically administered thrombolytic therapy over no such therapy. • In most patients with acute PE not associated with hypotension, recommend against systemically administered thrombolytic therapy. • In patients with a proximal DVT of the leg or PE provoked by surgery, treatment with anticoagulation for three months is recommended over (i) treatment of a shorter period, (ii) treatment of a longer time-limited period (e.g., six, 12, or 24 months), or (iii) extended therapy (no scheduled stop date). • In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, treatment with anticoagulation for three months is recommended over (i) treatment of a shorter period and (ii) treatment of a longer time-limited period (e.g., six, 12, or 24 months). Treatment with anticoagulation for three months is suggested over extended therapy if there is a low or moderate bleeding risk, and treatment for three months is recommended over extended therapy if there is a high risk of bleeding. • In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, treatment with anticoagulation for three months is suggested over treatment of a shorter period, treatment with anticoagulation for three months is recommended over treatment of a longer time-limited period (e.g., six, 12, or 24 months), and treatment with anticoagulation for three months is recommended over extended therapy (no scheduled stop date). • In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, treatment with anticoagulation for at least three months is recommended over treatment of a shorter duration), and treatment with anticoagulation for three months is recommended over treatment of a longer time-limited period (e.g., six, 12, or 24 months). • In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk, extended anticoagulant therapy (no scheduled stop date) is suggested over three months of therapy, and (ii) high bleeding risk, three months of anticoagulant therapy is recommended over extended therapy (no scheduled stop date). • In patients with a second unprovoked VTE and who have a (i) low bleeding risk, extended anticoagulant therapy (no scheduled stop date) is recommended over three months; (ii) moderate bleeding risk, extended anticoagulant therapy is suggested over three months of therapy; or (iii) high bleeding risk, three months of anticoagulant therapy is suggested over extended therapy (no scheduled stop date).

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	• In patients with "cancer-associated thrombosis" and who (i) do not have a high bleeding risk, extended anticoagulant therapy (no scheduled stop date) is recommended over three months of therapy, or (ii) have a high bleeding risk, extended anticoagulant therapy (no scheduled stop date) is suggested over three months of therapy. <u>Aspirin for extended treatment of VTE</u> • In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin is suggested over no aspirin to prevent recurrent VTE. <u>Whether to anticoagulate subsegmental PE</u> • In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE, clinical surveillance is suggested over anticoagulation or (ii) high risk for recurrent VTE, anticoagulation is suggested over clinical surveillance. <u>Treatment of acute PE out of the hospital</u> • In patients with low-risk PE and whose home circumstances are adequate, treatment at home or early discharge is suggested over standard discharge (e.g., after the first five days of treatment). <u>Systemic thrombolytic therapy for PE</u> • In patients with acute PE associated with hypotension (e.g., systolic BP <90 mm Hg) who do not have a high bleeding risk, systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension, systemically administered thrombolytic therapy is NOT recommended. • In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, systemically administered thrombolytic therapy is suggested over no such therapy. <u>Thrombolytic therapy in patients with upper extremity DVT</u> • In patients with acute upper extremity DVT (UEDVT) that involves the axillary or more proximal veins, anticoagulant therapy alone is suggested over thrombolysis. • In patients with UEDVT who undergo thrombolysis, the same intensity and duration of anticoagulant therapy as in patients with UEDVT who do not undergo thrombolysis is recommended. <u>Management of recurrent VTE on anticoagulant therapy</u> • In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), switching to treatment with LMWH at least temporarily is suggested. • In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), increasing the dose of LMWH by about one-quarter to one-third is suggested. • Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy. A temporary switch to LMWH will usually be for at least one month.

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American College of Cardiology/American Heart Association: **Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease (2016)**[15]	Recommendations for Antiplatelet Agents: • Antiplatelet therapy with aspirin alone (range 75 to 325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce myocardial infarction (MI), stroke, and vascular death in patients with symptomatic peripheral artery disease (PAD). • In asymptomatic patients with PAD (Ankle Brachial Index (ABI) ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death. • In asymptomatic patients with borderline ABI (0.91 to 0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain. • The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established. • DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization. • The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain. Recommendations for Statin Agents: • Treatment with a statin medication is indicated for all patients with PAD. Recommendations for Antihypertensive Agents: • Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. • The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD. Recommendations for Smoking Cessation: • Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit. • Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program. • Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places. Recommendations for Glycemic Control: • Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team. • Glycemic control can be beneficial for patients with critical limb ischemia (CLI) to reduce limb-related outcomes. Recommendations for Oral Anticoagulation: • The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain. • Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD. Recommendations for Cilostazol: • Cilostazol is an effective therapy to improve symptoms and increase walking

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	distance in patients with claudication. Recommendations for Pentoxifylline: Pentoxifylline is not effective for treatment of claudication.

American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2021)[16]**	Recommendations for Nonvalvular Atrial Fibrillation:
	• For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (~30 days) for AF is reasonable within six months of the index event.
	• VKA therapy, apixaban, dabigatran and rivaroxaban are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent.
	  ○ Selection of agent should be individualized based on risk factors, cost, tolerability, patient preference, drug interactions and other characteristics including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.
	• Target INR for patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent or permanent AF on VKA therapy is 2.5 (range 2.0 to 3.0).
	• Combination oral anticoagulation (warfarin or a newer agent) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA.
	  ○ Combination therapy is reasonable in patients with clinically apparent coronary artery disease particularly an acute coronary syndrome or stent placement.
	• For patients with ischemic stroke or TIA and AF who unable to take oral anticoagulants, aspirin alone is recommended.
	  ○ Adding clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable.
	• For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms.
	• In the presence of high risk for hemorrhagic conversion, it is reasonable to delay initiation of oral anticoagulation beyond 14 days.
	• For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent) is reasonable, depending on perceived risk for thromboembolism and bleeding.
	• The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain.
	
	Recommendations for Acute MI and LV Thrombus:
	• Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months is recommended in most patients with ischemic stroke or TIA in this setting.
	  ○ Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the American College of Chest Physicians.
	• Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging.
	• In patients with stroke or TIA and new LV thrombus (<3 months), the safety of anticoagulation with a direct oral anticoagulant to reduce risk of recurrent stroke is uncertain.
	• In patients with stroke or TIA in the setting of acute anterior MI with reduced

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	ejection fraction <50% but not evidence of LV thrombus, empirical anticoagulation for at least three months might be considered to reduce the risk of recurrent cardioembolic stroke Recommendations for Cardiomyopathy: • In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus, anticoagulant therapy with a VKA is recommended for ≥3 months. • In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) and aspirin is reasonable in the absence of major contraindications. • In patients with ischemic stroke or TIA in the setting of LV noncompaction, treatment with VKA therapy can be beneficial to reduce the risk of recurrent stroke. In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized. • In patients with stroke or TIA and LVADs, treatment with dabigatran instead of warfarin for the primary or secondary prevention of ischemic stroke or TIA causes harm. Recommendations for Mitral Stenosis, Mitral Regurgitation, Mitral Prolapse, Mitral Annular Calcification, and Aortic Valve Disease: • In patients with VHD (except moderate to severe mitral stenosis or a mechanical heart valve), ischemic stroke or TIA, and AF, DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin therapy. • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with INR target of 2.5 (range, 2.0 to 3.0) is recommended. • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (e.g., carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered instead of antiplatelet therapy. • For patients with rheumatic mitral valve disease who are prescribed VKA therapy after an ischemic stroke or TIA, antiplatelet therapy should not be routinely added. • For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered. • For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended. • For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification. • For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse. Recommendations for Prosthetic Heart Valves: • For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0 to 3.0). • For patients with a mechanical mitral valve and a history of ischemic stroke or

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	TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5 to 3.5). • For patients with a mechanical aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/day to VKA therapy is recommended. • For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/day or increasing the target INR, depending on bleeding risk. • For patients with a bioprosthetic aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and no other indication for anticoagulation therapy beyond three to six months form the valve placement, long-term therapy with aspirin 75 to 100 mg/day is recommended in preference to long-term anticoagulation. • For patients with a bioprosthetic aortic or mitral valve who have a TIA, ischemic stroke, or systemic embolism despite antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered. <u>Recommendations for Noncardioembolic Stroke or TIA</u>: • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. • Aspirin (50 to 325 mg/day) monotherapy, clopidogrel 75 mg daily, or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. • Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole. This recommendation also applies to patients who are allergic to aspirin. • For patients with recent minor noncardioembolic ischemic stroke or high-risk TIA, DAPT (aspirin plus clopidogrel) should be initiated within 12 to 24 hours of symptom onset and at least within seven days of onset. Therapy should be continued for 21 to 90 days, followed by single agent platelet therapy to reduce the risk of recurrent stroke. • For patients with recent minor to moderate stroke, high-risk TIA< or symptomatic intracranial or extracranial ≥30% stenosis of an artery, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events. • The selection of an antiplatelet agent should be individualized on the basis of patient risk facto profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics. • The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for two to three years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA). • For patients who have an ischemic stroke or TIA while taking aspirin, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established. • For patients with a history of ischemic stroke or TIA, AF and coronary artery disease, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet or

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	VKA therapy. • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. • The continued use of DAPT (aspirin plus clopidogrel) for >90 days or the use of triple antiplatelet therapy is associated with excess risk of hemorrhage.
American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[17]**	<u>Early hospital care- standard medical therapies</u> • Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. • Anti-ischemic and analgesic medications o Nitrates ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every five minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue beta-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to beta-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the

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	absence of contraindications, after appropriate use of beta-clockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when beta-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. ▪ Fibrinolytic therapy in patients with definite NSTE-ACS

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	Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least two to four hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. Late hospital care, hospital discharge, and posthospital discharge care • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or

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	unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guideline for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2020)[18]**	<u>Pharmacological treatment of ischemia</u> • Sublingual or intravenous nitrates and early initiation of beta-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • Continuation of chronic beta-blocker therapy is recommended unless the patient is in overt heart failure • Sublingual or intravenous nitrates are recommended to relieve angina; intravenous treatment is recommended in patients with recurrent angina, uncontrolled hypertension, or signs of heart failure. • In patients with suspected/confirmed vasospastic angina, calcium channel blockers, and nitrates should be considered and beta-blockers avoided.

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	Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes
	• Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150 to 300 mg (in aspirin-naïve patients) and a maintenance dose of 75 to 100 mg/day long-term regardless of treatment strategy.
	• A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risks of bleeds.
	  o Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindication, for all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).
	  o Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. Prasugrel should be considered in preference to ticagrelor in NSTE-ACS patients who proceed to PCI.
	  o Clopidogrel (300 to 600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.
	• $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after DES implantation may be considered in patients deemed at high bleeding risk.
	• Pre-treatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy.
	• It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known.
	• It is not recommended to administer prasugrel in patients whom coronary anatomy is not known.
	• GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.
	• Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI.
	• It is not recommended to administer GPIIb/IIIa inhibitors in patients whom coronary anatomy is not known.
	• $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of the ischemic and bleeding risks of the patient.
	
	Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes
	• Parenteral anticoagulation is recommended at the time of diagnosis according to both ischemic and bleeding risks.
	• Fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy.
	• Bivalirudin is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI.
	• UFH is recommended in patients undergoing PCI who did not receive any anticoagulant.
	• In patients on fondaparinux undergoing PCI, a single intravenous bolus of UFH is recommended during the procedure.
	• Enoxaparin or UFH are recommended when fondaparinux is not available.
	• Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated for PCI with subcutaneous enoxaparin.
	• Additional activated clotting time-guided intravenous boluses of UFH during

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	PCI may be considered following initial UFH treatment. • Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated. • Crossover between UFH and LMWH is not recommended. • In NSTEMI patients with no prior stroke/TIA and at high ischemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation. <u>Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation</u> • In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a $CHADS_2$-VASc score ≥2, recent VTE, mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. • An early invasive coronary angiography (within 24 hours) should be considered in moderate- to high-risk patients, irrespective of oral anticoagulant exposure, to expedite treatment allocation (medical vs PCI vs CABG) and to determine optimal antithrombotic regimen. • Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to oral anticoagulation before coronary angiography is not recommended. • During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all non-vitamin K antagonist oral anticoagulants (NOACs) and if INR is <2.5 in VKA-treated patients. • Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. • Periprocedural DAPT administration consisting of aspirin and clopidogrel up to one week is recommended • Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months • Following coronary stenting, dual (oral) antiplatelet therapy (DAPT) including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with non-ST-elevation acute coronary syndromes and atrial fibrillation with a $CHADS_2$-VASc score of 1 (in males) or 2 (in females). • If at low bleeding risk (HAS-BLED ≤2), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for six months, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months. • If at high bleeding risk (HAS-BLED ≥3), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for one month, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months irrespective of the stent type. • Dual therapy with oral anticoagulant and clopidogrel may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis). • The use of ticagrelor or prasugrel as part of triple therapy is not recommended. • In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year. <u>Recommendations for post-interventional and maintenance treatment</u> • In patients with NSTE-ACS with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding. • Adding a second anti-thrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a moderate to high risk of ischemic events and without increased risk of major bleeding.

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	• After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after three months should be considered • After stent implantation in patients undergoing DAPT, stopping aspirin after three to six months should be considered, depending on balance between ischemic and bleeding risk. • De-escalation of $P2Y_{12}$ inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.
American College of Cardiology Foundation/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[19]	<u>Antiplatelet therapy to support primary PCI for STEMI</u> • Aspirin 162 to 325 mg should be given before primary PCI. • After PCI, aspirin should be continued indefinitely. • A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg. • $P2Y_{12}$ inhibitor therapy should be given for one year to patients with STEMI who receive a stent (bare-metal or drug-eluting) during primary PCI using clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily. • It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI. • It is reasonable to start treatment with an IV GP IIb/IIIa receptor antagonist such as abciximab, high bolus-dose tirofiban or double-bolus eptifibatide at the time of primary PCI (with or without stenting or clopidogrel pre-treatment) in selected patients with STEMI who are receiving UFH. • It may be reasonable to administer IV GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended. • It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI. • Continuation of a $P2Y_{12}$ inhibitor beyond one year may be considered in patients undergoing drug-eluting stent placement. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. <u>Anticoagulant therapy to support primary PCI</u> • For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended: UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered or bivalirudin with or without prior treatment with UFH. • In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist. • Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis. <u>Adjunctive antiplatelet therapy with fibrinolysis</u> • Aspirin (162- to 325-mg loading dose) and clopidogrel (300 mg loading dose for ≤75 year of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy. • Aspirin should be continued indefinitely and clopidogrel (75 mg daily) should be continued for at least 14 days and up to one year in patients with STEMI who receive fibrinolytic therapy. • It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses after fibrinolytic therapy.

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	Adjunctive anticoagulant therapy with fibrinolysis • Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the hospitalization, up to eight days or until revascularization if performed. • Recommended regimens include UFH administered as a weight-adjusted IV bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularization; enoxaparin administered according to age, weight, and creatinine clearance, given as an IV bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to eight days or until revascularization; or fondaparinux administered with initial IV dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 mL/min, for the duration of the index hospitalization, up to eight days or until revascularization. Antiplatelet therapy to support PCI after fibrinolytic therapy • After PCI, aspirin should be continued indefinitely. • Clopidogrel should be provided as a 300 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy; a 600 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy; and a dose of 75 mg daily should be given after PCI. • After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses. • Prasugrel, in a 60 mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent. • Prasugrel, in a 10 mg daily maintenance dose, is reasonable after PCI. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. Anticoagulant therapy to support PCI after fibrinolytic therapy • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with IV UFH, additional boluses of IV UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior eight hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between eight and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given.

European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with Persistent ST-segment Elevation (2017)[20]**	Periprocedural pharmacotherapy
	• Platelet inhibition
	  ○ Patients undergoing primary percutaneous coronary intervention (PCI) should receive dual antiplatelet therapy (DAPT), a combination of aspirin and a $P2Y_{12}$ inhibitor, and a parenteral anticoagulant.
	  ○ A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.

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	○ Aspirin (oral of intravenous if unable to swallow) is recommended as soon as possible for all patients without contraindications. ○ GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication. ○ Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors. • Anticoagulant therapy ○ Anticoagulant options for primary PCI include unfractionated heparin (UFH), enoxaparin, and bivalirudin. ○ Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI. ○ Routine use of UFH is recommended. ○ In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI. ○ Routine use of enoxaparin intravenous should be considered. ○ Routine use of bivalirudin should be considered. ○ Fondaparinux is not recommended for primary PCI. <u>Maintenance antithrombotic strategy after ST-elevation myocardial infarction</u> • Antiplatelet therapy with low-dose aspirin (75 to 100 mg) is indicated. • DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy should be considered for one to six months (according to a balance between the estimated risk of recurrent coronary events and bleeding). • DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding. • In patients with left ventricular (LV) thrombus, anticoagulation should be administered for up to six months guided by repeated imaging. • In high ischemic-risk patients who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice daily on top of aspirin for longer than 12 months may be considered for up to three years. • In low bleeding risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. <u>Routine therapies in the acute, subacute, and long-term phases</u> • Beta-blockers ○ Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF ≤40% unless contraindicated. ○ Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without

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	contraindications, with no signs of acute heart failure, and with an SBP >120 mmHg. ○ Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindication. ○ Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia. • Lipid-lowering therapies ○ It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term. ○ An LDL-C goal of <70 mg/dL or a reduction of at least 50% if the baseline LDL-C is between 70 to 135 mg/dL is recommended. ○ It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation. ○ In patients with LDL-C ≥70 mg/dL despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. • ACE inhibitors/ARBs ○ ACE inhibitors are recommended, starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct. ○ An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors. ○ ACE inhibitors should be considered in all patients in the absence of contraindications. • Mineralocorticoid receptor antagonists ○ Mineralocorticoid receptor antagonists are recommended in patients with an LVEF ≤40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalemia.
American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions: **2021 Guideline for Coronary Artery Revascularization (2021)**[21]	Pharmacotherapy in Patients Undergoing PCI • In patients undergoing PCI, a loading dose of aspirin, followed by a daily dosing, is recommended to reduce ischemic events. • In patients with ACS undergoing PCI, a loading dose of $P2Y_{12}$ inhibitor, followed by daily dosing, is recommended to reduce ischemic events. • In patients with SIHD undergoing PCI, a loading dose of clopidogrel, followed by daily dosing is recommended to reduce ischemic events. • In patients undergoing PCI within 24 hours after fibrinolytic therapy, a loading dose of 300 mg of clopidogrel, followed by daily dosing, is recommended to reduce ischemic events. • In patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischemic events, including stent thrombosis. • In patients <75 years of age undergoing PCI within 24 hours after fibrinolytic therapy, ticagrelor may be a reasonable alternative to clopidogrel to reduce ischemic events. • In patients undergoing PCI who have a history of stroke or transient ischemic attack, prasugrel should not be administered. Antiplatelet Pharmacotherapy in Patients Undergoing CABG • In patients undergoing CABG who are already taking daily aspirin preoperatively, it is recommended that they continue taking aspirin until the time of surgery to reduce ischemic events.

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	• In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours before surgery to reduce major bleeding complications. • In patients undergoing CABG, discontinuation of short-acting glycoprotein IIb/IIIa inhibitors for four hours and abciximab for 12 hours before surgery is recommended to reduce the risk of bleeding and transfusion. • In patients undergoing elective CABG who receive $P2Y_{12}$ receptor inhibitors before surgery, it is reasonable to discontinue clopidogrel for five days, ticagrelor for three days and prasugrel for seven days before CABG to reduce risk of major bleeding and blood product transfusion. • In patients undergoing elective CABG who are not already taking aspirin, the initiation of aspirin in the immediate pre-operative period is not recommended. <u>Antiplatelet Pharmacotherapy in Patients After Revascularization</u> • In selected patients undergoing PCI, shorter duration dual antiplatelet therapy (one to three months) is reasonable, with subsequent transition to $P2Y_{12}$ inhibitor monotherapy to reduce the risk of bleeding events. • In patients undergoing CABG, aspirin (100 to 325 mg daily) should be initiated within six hours postoperatively and then continued indefinitely to reduce the occurrence of SVG closure and adverse cardiovascular events. • In selected patients undergoing CABG, dual antiplatelet therapy with aspirin and ticagrelor or clopidogrel for one year may be reasonable to improve vein graft patency compared with aspirin alone. • In patients with atrial fibrillation who are undergoing PCI and are taking oral anticoagulant therapy, it is recommended to discontinue aspirin treatment after one to four weeks while maintaining $P2Y_{12}$ inhibitors in addition to a non-vitamin K oral anticoagulant (rivaroxaban, dabigatran, apixaban or edoxaban) or warfarin to reduce the risk of bleeding. • In patients with atrial fibrillation who are undergoing PCI, are taking oral anticoagulant therapy, and are treated with DAPT or a $P2Y_{12}$ inhibitor monotherapy, it is reasonable to choose a non-vitamin K oral anticoagulant over warfarin to reduce the risk of bleeding.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)**[22]	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity.

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	• For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary

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	artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk.

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	Recommendations for aspirin use • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
National Institute for Health and Clinical Excellence: **Clopidogrel and Modified-Release Dipyridamole for the Prevention of Occlusive Vascular Events (2010)**[23]	• This guidance applies to people who have had an occlusive vascular event, or who have established peripheral arterial disease. This guidance does not apply to people who have had, or are at risk of, a stroke associated with AF, or who need treatment to prevent occlusive events after coronary revascularization or carotid artery procedures. • For people who have had an ischemic stroke, clopidogrel is recommended as a treatment option. For people who have a contraindication or intolerance to clopidogrel, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to both clopidogrel and aspirin, modified-release dipyridamole alone is recommended as a treatment option. • For people who have had a TIA, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to aspirin, modified-release dipyridamole alone is recommended as a treatment option. • For people who have had a MI, clopidogrel is recommended only when treatment with aspirin is contraindicated or not tolerated. • For people with peripheral arterial disease, clopidogrel is recommended as a treatment option. • For people with multi-vascular disease, clopidogrel is recommended as a treatment option. • Treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2014)**[24]	Medical therapy to prevent MI and death in patients with stable IHD • Aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications. • Treatment with clopidogrel is a reasonable option when aspirin in contraindicated. • Dipyridamole should not be used as antiplatelet therapy. • Beta-blocker therapy should be initiated and continued for three years in all patients with normal left ventricular (LV) function following MI or acute coronary syndromes. • Metoprolol succinate, carvedilol, or bisoprolol should be used for all patients with systolic LV dysfunction (ejection fraction ≤40%) with heart failure or prior MI, unless contraindicated. • ACE inhibitors should be prescribed in all patients with stable IHD who also have hypertension, diabetes, LV systolic dysfunction (ejection fraction ≤40%), and/or chronic kidney disease, unless contraindicated. • Angiotensin-receptor blockers (ARBs) are recommended for patients with stable IHD who have hypertension, diabetes, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. • Patients should receive an annual influenza vaccine.

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	Medical therapy for relief of symptoms in patients with stable IHD • Beta-blockers are recommended as initial therapy for relief of symptoms. • Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects. • Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful. • Nitroglycerin or nitroglycerin spray should be used for immediate relief of angina. • Ranolazine is a fourth-line agent reserved for patients who have contraindications to, do not respond to, or cannot tolerate β-blockers, calcium-channel blockers, or long-acting nitrates.
European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)**[25]	Pharmacological management of stable coronary artery disease (CAD) patients • The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events. • Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention. • It is recommended to educate patients about the disease, risk factors and treatment strategy. • It is indicated to review the patient's response soon after starting therapy. • Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding. • Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended • ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events • Angina/ischemia relief: o Short-acting nitrates are recommended. o First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms o o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. • Event prevention: o Low-dose aspirin daily is recommended in all stable CAD patients. o Clopidogrel is indicated as an alternative in case of aspirin intolerance. o Statins are recommended in all stable CAD patients.

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	○ It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes). <u>Treatment in patients with microvascular angina</u> • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • ß-blockers are recommended as a first-line treatment. • Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT). • Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only. • Platelet function testing or genetic testing may be considered in specific or high risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after 2nd generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk.

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	• DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.

American Heart Association/American College of Cardiology Foundation: **Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2011 Update (2011)[26]**	<u>Antiplatelet agents/anticoagulants</u>
	• Aspirin 75 to 162 mg daily is recommended in all patients with coronary artery disease unless contraindicated.
	  ◦ Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.
	  ◦ Combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease.
	• A $P2Y_{12}$ receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement.
	  ◦ For patients receiving a bare-metal stent or drug-eluting stent during PCI or ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily or ticagrelor 90 mg twice daily should be given for at least 12 months.
	  ◦ If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy after stent implantation, earlier discontinuation (e.g., 12 months) is reasonable. The risk for serious cardiovascular events because of early discontinuation of thienopyridines is greater for patients with drug-eluting stents than those with bare-metal stents.
	  ◦ After PCI, it is reasonable to use aspirin 81 mg daily in preference to higher maintenance doses.
	• For patients undergoing CABG, aspirin should be started within six hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg daily for one year appear to be efficacious.
	  ◦ For patients undergoing CABG, clopidogrel (75 mg daily) is a reasonable alternative in patients who are intolerant of or allergic to aspirin.
	• In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75 to 325 mg daily), clopidogrel alone (75 mg daily) or the combination of aspirin plus dipyridamole ER (25 mg and 200 mg twice daily, respectively) should be started and continued.
	• For patients with symptomatic atherosclerotic PAD of the lower extremity, antiplatelet therapy with aspirin (75 to 325 mg daily) or clopidogrel (75 mg daily) should be started and continued.
	  ◦ The benefits of aspirin in patients with asymptomatic PAD of the lower extremities are not well established.
	• Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other VKA to treat patients with atherosclerosis.
	  ◦ If there is a compelling indication for anticoagulant therapy, such as AF, prosthetic heart valve, left ventricular thrombus or concomitant venous thromboembolic disease, warfarin should be administered in addition to the low-dose aspirin (75 to 81 mg daily).
	  ◦ For patients requiring warfarin, therapy should be administered to achieve the recommended INR for the specific condition.

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	• Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.
European Association for Cardiovascular Prevention and Rehabilitation: **European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2021)**[27]	<u>Antiplatelet therapy</u> • Antiplatelet therapy is not recommended in individuals free from cardiovascular disease (CVD), due to the increased risk of major bleeding. • In patients with ischemic stroke or transient ischemic attack (TIA), prevention with antithrombotics is recommended. If the event is a non-cardioembolic ischemic stroke or TIA use of antiplatelets is recommended. If the event is a cardioembolic stroke or TIA use of anticoagulants is recommended. • In acute coronary syndromes, a $P2Y_{12}$ inhibitor for 12 months is recommended in addition to aspirin, unless there are contraindications such as excessive risk of bleeding. • $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after drug-eluting stent (DES) implantation may be considered in patients deemed at high bleeding risk. • In patients with chronic coronary syndrome, clopidogrel 75 mg daily is recommended, in addition to aspirin for six months following stenting. Shorter duration considered if increased risk or occurrence of life-threatening bleeding. • $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of ischemic and bleeding risks of the patient. • In the chronic phase (>12 months) after myocardial infarction (MI), aspirin is recommended. • In patients with non-cardioembolic ischemic stroke or transient ischemic attack (TIA), prevention with aspirin only, or dipyridamole plus aspirin or clopidogrel alone is recommended. • In patients with minor ischemic stroke or TIA, DAPT with aspirin and clopidogrel or with aspirin and ticagrelor, for three weeks after event should be considered • Prasugrel is not recommended in patients with stable coronary artery disease (CAD). Ticagrelor is not recommended in patients with stable CAD without a previous acute coronary syndrome (ACS). • Antiplatelet therapy is recommended in patients with symptomatic lower extremity artery disease.
The American College of Cardiology/ American Heart Association: **Practice Guidelines for the Management of Patients with Peripheral Artery Disease (2013)**[28]	<u>Exercise and lower extremity peripheral artery disease (PAD) rehabilitation</u> • A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. • Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times/week for a minimum of 12 weeks. • The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication. <u>Smoking cessation</u> • Patients who are smokers or former smokers should be asked about status of tobacco use at every visit. Patients with lower extremity PAD who use tobacco should be advised to stop smoking. • Patients should be provided with counseling and assistance with developing a plan for smoking cessation. • One or more of the following pharmacological therapies should be offered if not contraindicated: varenicline, bupropion and nicotine replacement therapy. <u>Antiplatelet and antithrombotic drugs</u> • Antiplatelet therapy is indicated to reduce the risk of MI, stroke and vascular

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	death in patients with symptomatic atherosclerotic lower extremity PAD and in asymptomatic patients with ankle brachial index ≤0.90. The usefulness of antiplatelet therapy is not well established in asymptomatic patients with ankle brachial index between 0.91 and 0.99. • Aspirin (75 to 325 mg/day) is recommended to reduce the risk of cardiovascular events. Clopidogrel (75 mg/day) is recommended as an alternative to aspirin. • Combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD who are at high cardiovascular risk and not at increased risk of bleeding. • The addition of warfarin to antiplatelet therapy is of no proven benefit and is potentially harmful due to increased risk of major bleeding. <u>Medical and pharmacological treatment for claudication</u> • Cilostazol (100 mg orally twice daily) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure). • A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure). • Pentoxifylline (400 mg three times daily) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication. • The clinical effectiveness of pentoxifylline as therapy for intermittent claudication is marginal and not well established. • The effectiveness of L-arginine for patients with intermittent claudication is not well established. • The effectiveness of propionyl L-carnitine as a therapy to improve walking distance in patients with intermittent claudication is not well established. • The effectiveness of ginkgo biloba as a therapy to improve walking distance in patients with intermittent claudication is not well established. • Oral vasodilator prostaglandins such as beraprost* and iloprost are not effective medications to improve walking distance in patients with intermittent claudication. • Vitamin E is not recommended as a treatment for patients with intermittent claudication. • Chelation (e.g. ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects.
American College of Cardiology/American Heart Association: **Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease (2016)**[29]	<u>Recommendations for Antiplatelet Agents:</u> • Antiplatelet therapy with aspirin alone (range 75 to 325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce myocardial infarction (MI), stroke, and vascular death in patients with symptomatic peripheral artery disease (PAD). • In asymptomatic patients with PAD (Ankle Brachial Index (ABI) ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death. • In asymptomatic patients with borderline ABI (0.91 to 0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain. • The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established. • DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.

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	• The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain. <u>Recommendations for Statin Agents:</u> • Treatment with a statin medication is indicated for all patients with PAD. <u>Recommendations for Antihypertensive Agents:</u> • Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. • The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD. <u>Recommendations for Smoking Cessation:</u> • Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit. • Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program. • Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places. <u>Recommendations for Glycemic Control:</u> • Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team. • Glycemic control can be beneficial for patients with critical limb ischemia (CLI) to reduce limb-related outcomes. <u>Recommendations for Oral Anticoagulation:</u> • The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain. • Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD. <u>Recommendations for Cilostazol:</u> • Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication. <u>Recommendations for Pentoxifylline:</u> • Pentoxifylline is not effective for treatment of claudication.
European Society of Cardiology, Task Force on the Use of Antiplatelet Agents in Patients With Atherosclerotic Cardiovascular Disease: **Expert Consensus Document on the Use of Antiplatelet Agents (2004)**[30]	<u>Major recommendations for individual antiplatelet agents</u> Aspirin: • Aspirin once-daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. • Because of gastrointestinal toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting. • The available evidence supports daily doses of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients (e.g., ≥3% per annum). • In clinical situations where an immediate antithrombotic effect is required (such as in ACS or in acute ischemic stroke), a loading dose of 160 to 300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of

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	thromboxane A2-dependent platelet aggregation. • No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient. • The routine use of proton pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75 to 100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting. • Nonsteroidal anti-inflammatory drugs have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin. • Because of potential pharmacodynamic interactions between traditional nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) and aspirin, patients treated with low-dose aspirin requiring nonsteroidal ant-inflammatory drug therapy may benefit from the use of selective cyclooxegenase-2 inhibitors. Ticlopidine: • The role of ticlopidine in the present therapeutic armamentarium is uncertain. • Although there are no large head-to-head comparisons between the two thienopyridines, indirect comparisons are highly suggestive of a lower burden of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine. • In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent MI. Clopidogrel: • Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain and the drug has not been granted a claim of "superiority" vs aspirin by regulatory authorities. • Clopidogrel 75 mg/day is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a contraindication to low-dose aspirin. • The results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial have led to Food and Drug Administration approval of a new indication for clopidogrel in patients with NSTE ACS. A loading dose of 300 mg clopidogrel should be used in this setting, followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of PCI, length of clopidogrel treatment and combination with GP IIb/IIIa antagonists. Dipyridamole: • Although the combination of low-dose aspirin and dipyridamole ER (200 mg twice-daily) is considered an acceptable option for initial therapy of patients with noncardioembolic cerebral ischemic events, there is no basis to recommend this combination in patients with ischemic heart disease.
European Society of Cardiology/ European Association for Cardio-Thoracic Surgery: **2017 Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease (2017)**[31]	Recommendations on $P2Y_{12}$ inhibitor selection and timing • In patients with acute coronary syndrome (ACS), ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications. • In patients with ACS undergoing percutaneous coronary intervention (PCI), prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) or initially conservatively managed ST-elevation myocardial infarction (STEMI) if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high risk of life-threatening bleeding or other contraindications. • Pre-treatment with a $P2Y_{12}$ inhibitor is generally recommended in patients in

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	whom coronary anatomy is known and the decision to proceed to PCI is made as well as in patients with STEMI. • In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established. • In patients with stable coronary artery disease (CAD), pre-treatment with clopidogrel may be considered if the probability of PCI is high. • Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for an oral anticoagulant. • Clopidogrel (300 mg loading dose in patients aged <75, 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis. • Ticagrelor or prasugrel on top of aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI, taking into account the ischemic (e.g. high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding (e.g. according to PRECISE-DAPT score) risks. • In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel. <u>Switching between oral $P2Y_{12}$ inhibitors</u> • In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindications to ticagrelor exist. • Additional switching between oral $P2Y_{12}$ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms. <u>Measures to minimize bleeding while on dual antiplatelet therapy</u> • Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator. • In patients treated with DAPT, a daily aspirin dose of 75 to 100 mg is recommended. • A proton pump inhibitor in combination with DAPT is recommended. • Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended. <u>Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention</u> • In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥25). <u>Dual antiplatelet therapy duration in patients with acute coronary syndrome undergoing medical therapy management</u> • In patients with ACS who are managed with medical therapy alone and treated with DAPT, it is recommended to continue $P2Y_{12}$ inhibitor therapy (either ticagrelor or clopidogrel) for 12 months. • Ticagrelor is recommended over clopidogrel, unless the bleeding risk outweighs the potential ischemic benefit. • Prasugrel is not recommended in medically managed ACS patients.

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	Dual antiplatelet therapy in patients undergoing elective cardiac and non-cardiac surgery • It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively. • It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[32]	Pharmacological treatments indicated in patients with New York Heart Association (NYHA) Class II-IV heart failure with reduced ejection fraction • An angiotensin-converting enzyme (ACE) inhibitor is recommended, in addition to a beta-blocker, for symptomatic patients with heart failure with reduced ejection fraction (HFrEF) to reduce the risk of heart failure (HF) hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE inhibitor/angiotensin receptor neprilysin inhibitor (ARNI), a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with left ventricle ejection fraction (LVEF) ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor or angiotensin receptor blocker (ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a beta-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated left ventricle in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic

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	patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a beta-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin are recommended in patients with diabetes at high risk • of CV disease or with CV disease in order to prevent HF hospitalizations. • Counseling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and systolic blood pressure (SBP) >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve

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	symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with low molecular weight heparin) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the platelet-aggregation 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 Platelet-Aggregation Inhibitors[1-7]

Indication	Cilostazol	Clopidogrel	Prasugrel	Ticagrelor	Vorapaxar
Acute Coronary Syndromes					
Reduce the rate of myocardial infarction and stroke in patients with non-ST-segment elevation ACS (unstable angina/non-ST-elevation myocardial infarction), including patients who are to be managed medically and those who are to be managed with coronary revascularization		✔			
Reduce the rate of myocardial infarction and stroke in patients with acute ST-elevation myocardial infarction (STEMI) who are to be managed medically		✔			
Reduce the rate of cardiovascular death, MI, and stroke in patients with acute coronary syndrome or a history of MI and reduce the rate of stent thrombosis in patients who have been stented for treatment of ACS				✔	
Reduce the rate of MI or stroke in patients with coronary artery disease (CAD)				✔	
Reduce the risk of stroke in patients with acute ischemic stroke or high-risk transient ischemic stroke (TIA)				✔	
Reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD)					✔
Reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows: patients with unstable angina or NSTEMI OR patients with STEMI when managed with primary or delayed percutaneous coronary intervention			✔		
Atherothrombotic/Vascular Events					
Reduce the rate of MI and stroke in patients with established peripheral arterial disease or with a history of recent MI or recent stroke		✔			
Intermittent Claudication					
For the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance	✔				

IV. Pharmacokinetics

The pharmacokinetic parameters of the platelet-aggregation inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Platelet-Aggregation Inhibitors[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Cilostazol	87 to 100	95 to 98	Liver (% not reported)	Renal (74) Feces (20)	11 to 13
Clopidogrel	≥50	Not reported	Liver (% not reported)	Renal (50) Feces (46)	6
Prasugrel	79	98	Liver (% not reported)	Renal (68 to 70) Feces (25 to 27)	7 to 8
Ticagrelor	36	>99	Liver (% not reported)	Renal (26) Feces (58)	7
Vorapaxar	100	>99	Liver (% not reported)	Renal (25) Feces (58)	192

*Dipyridamole follows a two-compartment model.

V. Drug Interactions

Major drug interactions with the platelet-aggregation inhibitors are listed in Table 5. Concurrent use of platelet-aggregation inhibitors with non-steroidal anti-inflammatory drugs (NSAIDS) increases bleeding risk.[2]

Table 5. Major Drug Interactions with the Platelet-Aggregation Inhibitors[2]

Generic Name(s)	Interaction	Mechanism
Cilostazol, clopidogrel, prasugrel, ticagrelor, vorapaxar	Defibrotide	Concomitant use of defibrotide and a systemic antithrombotic agent is contraindicated as the pharmacodynamic activity of the antithrombotic agent may be enhanced, leading to an increased risk of bleeding.
Cilostazol, clopidogrel, prasugrel, ticagrelor, vorapaxar	SSRIs	Concurrent use may result in an increased risk of bleeding.
Cilostazol, ticagrelor	CYP3A4 inhibitors	Certain agents inhibit the metabolism (CYP3A4) of cilostazol leading to increased plasma concentrations of cilostazol and resulting in increased therapeutic and adverse effects.
Cilostazol	CYP2C19 inhibitors	These agents inhibit the metabolism (CYP2C19) of cilostazol leading to increased plasma concentrations of cilostazol and resulting in increased therapeutic and adverse effects.
Cilostazol	Amiodarone	Concurrent use of amiodarone and cilostazol may result in increased amiodarone and cilostazol exposure.
Cilostazol	Ginkgo	Concurrent use of cilostazol and ginkgo may result in increased bleeding risk.
Cilostazol	Nefazodone	Concurrent use of cilostazol and nefazodone may result in increased cilostazol exposure and increased risk of bleeding.
Clopidogrel	Calcium channel blockers	Concurrent use of calcium channel blockers and clopidogrel may result in decreased antiplatelet effect and increased risk of thrombotic events.
Clopidogrel	Opioid agonists	Concurrent use of clopidogrel and opioid agonists may result in reduced efficacy of clopidogrel.
Clopidogrel	Proton-pump Inhibitors	Proton pump inhibitors interfere with the metabolic conversion of clopidogrel at cytochrome P450 (CYP) 2C19 to its active

Generic Name(s)	Interaction	Mechanism
		metabolite, thus decreasing the antiplatelet activity of clopidogrel.
Clopidogrel	Ketoconazole	Ketoconazole may inhibit the isozymes (CYP3A4 and CYP3A5) that convert the prodrug clopidogrel to its active metabolite. If possible, avoid coadministration of these agents since the antiplatelet effect of clopidogrel may be inhibited.
Clopidogrel	Nifedipine	Concurrent use of clopidogrel and nifedipine may result in decreased antiplatelet effect and increased risk of thrombotic events.
Clopidogrel	Warfarin	The mechanism by which the risk of nonfatal and fatal bleeding may be increased with combined therapy is unknown. When indicated, coadminister clopidogrel and warfarin with caution. Closely monitor coagulation and the patient for bleeding events.
Ticagrelor	Strong 3A4 inducers	Concurrent use of ticagrelor and strong CYP3A4 inducers may result in decreased ticagrelor plasma concentrations.
Ticagrelor	Itraconazole	Concurrent use of itraconazole and ticagrelor may result in increased ticagrelor exposure.
Vorapaxar	Azole antifungals	Inhibition of vorapaxar metabolism (CYP3A4) by azole and related antifungal agents may elevate vorapaxar plasma concentrations, increasing the pharmacologic effects and risk of adverse reactions.
Vorapaxar	Protease inhibitors	Inhibition of vorapaxar metabolism (CYP3A4) by certain protease inhibitors may elevate vorapaxar plasma concentrations, increasing the pharmacologic effects and risk of adverse reactions.
Vorapaxar	Boceprevir, telaprevir	Inhibition of vorapaxar metabolism (CYP3A4) by HCV protease inhibitors may elevate vorapaxar plasma concentrations, increasing the pharmacologic effects and risk of adverse reactions.
Vorapaxar	Clarithromycin, telithromycin	Inhibition of vorapaxar metabolism (CYP3A4) by certain macrolide and related antibiotics may elevate vorapaxar plasma concentrations, increasing the pharmacologic effects and risk of adverse reactions.
Vorapaxar	Conivaptan	Inhibition of vorapaxar metabolism (CYP3A4) by conivaptan may elevate vorapaxar plasma concentrations, increasing the pharmacologic effects and risk of adverse reactions.
Vorapaxar	Nefazodone	Inhibition of vorapaxar metabolism (CYP3A4) by nefazodone may elevate vorapaxar plasma concentrations, increasing the pharmacologic effects and risk of adverse reactions.
Vorapaxar	Carbamazepine	Increased vorapaxar metabolism (CYP3A4) by carbamazepine may decrease vorapaxar plasma concentrations and pharmacologic effects.
Vorapaxar	Hydantoins	Increased vorapaxar metabolism (CYP3A4) by hydantoins may decrease vorapaxar plasma concentrations and pharmacologic effects.
Vorapaxar	Rifamycins	Increased vorapaxar metabolism (CYP3A4) by rifamycins may decrease vorapaxar plasma concentrations and pharmacologic effects.
Vorapaxar	St. John’s Wort	Increased vorapaxar metabolism (CYP3A4) by St. John's Wort may decrease vorapaxar plasma concentrations and pharmacologic effects.

VI. Adverse Drug Events

The most common adverse drug events reported with the platelet-aggregation inhibitors are listed in Table 6. The boxed warnings for the platelet-aggregation inhibitors are listed in Tables 7 through 11.

Table 6. Adverse Drug Events (%) Reported with the Platelet-Aggregation Inhibitors[1-7]

Adverse Events	Cilostazol	Clopidogrel	Prasugrel	Ticagrelor	Vorapaxar
Cardiovascular					
Atrial fibrillation/flutter	<2	1 to 3	3	4.2	-
Bradycardia	-	-	3	-	-
Cardiac arrest	<2	-	-	-	-
Cardiac failure	-	1 to 3	-	-	-
Chest pain	-	8	3	3.1	-
Congestive heart failure	<2	-	-	-	-
Edema	-	4	3	-	-
Hypertension	-	4	8	3.8	-
Hypotension	<2	-	4	3.2	-
Myocardial infarction/ischemia	<2	-	-	-	-
Nodal arrhythmia	<2	1 to 3	-	-	-
Palpitation	5 to 10	-	-	-	-
Peripheral edema	7 to 9	-	-	-	-
Postural hypotension	<2	-	-	-	-
QTc prolongation	<2	-	-	-	-
Supraventricular tachycardia	<2	-	-	-	-
Syncope	<2	1 to 3	-	-	-
Tachycardia	4	-	-	-	-
Torsades de pointes	<2	-	-	-	-
Ventricular tachycardia	<2	-	-	-	-
Central Nervous System					
Anxiety	-	1 to 3	-	-	-
Cerebral hemorrhage	-	<1	-	-	-
Cerebral infarction/ischemia	<2	-	-	-	-
Confusion	-	<1	-	-	-
Depression	-	4	-	-	2
Dizziness	9 to 10	2 to 6	4	4.5	-
Extremity pain	-	-	3	-	-
Fatigue	-	3	4	3.2	-
Fever	-	1 to 3	5	-	-

Adverse Events	Cilostazol	Clopidogrel	Prasugrel	Ticagrelor	Vorapaxar
Hallucination	<1	-	-	-	-
Headache	27 to 34	3 to 8	2	6.5	-
Insomnia	-	1 to 3	-	-	-
Pain	-	6	-	-	-
Subdural hematoma	<2	-	-	-	-
Vertigo	<3	1 to 3	-	-	-
Dermatologic					
Bullous eruption	-	<1	-	-	-
Eczema	-	1 to 3	-	-	-
Erythema multiforme	-	<1	-	-	-
Extradural hematoma	<2	-	-	-	-
Ischemic necrosis	-	<1	-	-	-
Lichen planus	-	<1	-	-	-
Maculopapular rash	-	<1	-	-	-
Pruritus	-	3	-	-	-
Rash	-	4	3	-	2
Stevens-Johnson syndrome	<2	-	-	-	-
Toxic epidermal necrolysis	-	<1	-	-	-
Urticaria	-	<1	-	-	-
Endocrine and Metabolic					
Diabetes mellitus	<2	-	-	-	-
Gout/hyperuricemia	<2	1 to 3	-	-	-
Hypercholesterolemia	4	-	7	-	-
Pancreatitis	-	<1	-	-	-
Gastrointestinal					
Abdominal pain	4 to 5	2 to 6	-	-	-
Abnormal stools	12 to 15	-	-	-	-
Colitis	<2	-	-	-	-
Constipation	-	1 to 3	-	-	-
Diarrhea	12 to 19	2 to 5	-	3.7	-
Duodenal ulcer	<2	-	2	-	-
Duodenitis	<2	-	-	-	-
Dyspepsia	6	2 to 5	-	-	-
Esophageal hemorrhage	<2	-	-	-	-
Esophagitis	<2	-	-	-	-
Flatulence	2 to 3	-	-	-	-

Adverse Events	Cilostazol	Clopidogrel	Prasugrel	Ticagrelor	Vorapaxar
Gastrointestinal hemorrhage	-	1 to 3	2	-	4
Nausea	6 to 7	3	5	4.3	-
Peptic ulcer	<2	-	-	-	-
Periodontal abscess	<2	-	-	-	-
Rectal bleeding	<2	-	-	-	-
Retroperitoneal hemorrhage	<2	<1	-	-	-
Vomiting	-	1 to 3	-	-	-
Genitourinary			-		
Cystitis	<2	1 to 3	-	-	-
Hematuria	-	<1	-	-	-
Urinary tract infection	-	3	-	-	-
Hematologic					
Agranulocytosis	<2	<1	-	-	-
Anemia	<2	1 to 3	2	-	5
Aplastic anemia	-	<1	-	-	-
Bleeding	-	4 to 5	-	8.7*, 85.8†	-
Epistaxis	-	3	-	-	-
Granulocytopenia	<2	<1	-	-	-
Hematoma	-	1 to 3	✔	-	-
Hemorrhage	<2	-	✔	-	3
Hypochromic anemia	-	<1	-	-	-
Iron deficiency	-	-	-	-	<2
Leukopenia	<2	<1	3	-	-
Neutropenia	-	<1	-	-	-
Pancytopenia	-	<1	-	-	-
Polycythemia	<2	-	-	-	-
Purpura	-	5	-	-	-
Thrombocytopenia	<2	<1	✔	-	-
Thrombosis	<2	-	-	-	-
Hepatic					
Acute liver failure	-	<1	-	-	-
Bilirubinemia	-	<1	-	-	-
Cholelithiasis	<2	-	-	-	-
Fatty liver	-	<1	-	-	-
Hepatic dysfunction	<2	-	✔	-	-
Hepatitis	-	<1	-	-	-

Adverse Events	Cilostazol	Clopidogrel	Prasugrel	Ticagrelor	Vorapaxar
Liver function test abnormalities	-	<3	-	-	-
Musculoskeletal					
Arthralgia	-	6	-	-	-
Arthritis	-	1 to 3	-	-	-
Back pain	6 to 7	6	5	3.6	-
Bursitis	<2	-	-	-	-
Leg cramps	-	1 to 3	-	-	-
Myalgia	2 to 3	-	-	-	-
Neuralgia	<2	1 to 3	-	-	-
Paresthesia	-	1 to 3	-	-	-
Weakness	-	1 to 3	-	-	-
Respiratory					
Asthma	<2	-	-	-	-
Bronchitis	-	4	-	-	-
Cough	3 to 4	3	4	4.9	-
Dyspnea	-	5	5	13.8	-
Epistaxis	-	-	6	-	-
Hemoptysis	-	<1	-	-	-
Hemothorax	-	<1	-	-	-
Intestinal pneumonitis	-	<1	-	-	-
Pharyngitis	7 to 10	-	-	-	-
Pneumonia	<2	-	-	-	-
Pulmonary hemorrhage	-	<1	-	-	-
Rhinitis	7 to 12	4	-	-	-
Other					
Allergic reaction	-	<1	✔	-	-
Anaphylactoid reaction/anaphylaxis	-	<1	-	-	-
Angioedema	-	<1	✔	-	-
Blindness	<2	-	-	-	-
Cataract	-	1 to 3	-	-	-
Conjunctivitis	-	1 to 3	-	-	-
Fever	-	<1	-	-	-
Flu symptoms	-	8	-	-	-
Hypersensitivity reaction	-	<1	-	-	-
Infection	10 to 14	-	-	-	-
Noncardiac chest pain	-	-	-	3.7	-

Adverse Events	Cilostazol	Clopidogrel	Prasugrel	Ticagrelor	Vorapaxar
Ocular/retinal hemorrhage	<2	<1	-	-	-
Retinopathy	-	-	-	-	<2
Serum sickness	-	<1	-	-	-
Vasculitis	-	<1	-	-	-

✔ Percent not specified.
- Event not reported.
*Non-coronary artery bypass graft-related bleeding.
†Coronary artier bypass graft-related bleeding.

Table 7. Boxed Warning for Cilostazol[1]

WARNING
Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. Cilostazol is contraindicated in patients with congestive heart failure of any severity.

Table 8. Boxed Warning for Clopidogrel[1]

WARNING
The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 system (CYP), primarily CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used an as aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

Table 9. Boxed Warning for Prasugrel[1]

WARNING
Prasugrel can cause significant, sometimes fatal, bleeding. Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients 75 years of age and older, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior myocardial infarction) in which its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery. When possible, discontinue prasugrel at least seven days prior to any surgery. Additional risk factors for bleeding include body weight less than 60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention, coronary artery bypass grafting, or other surgical procedures in the setting of prasugrel. If possible, manage bleeding without discontinuing prasugrel. Discontinuing prasugrel, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.

Table 10. Boxed Warning for Ticagrelor[1]

WARNING
Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding. Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage. Do not initiate therapy with ticagrelor in patients planning to undergo urgent coronary artery bypass graft (CABG) surgery. When possible, discontinue ticagrelor at least five days prior to any surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention, CABG, or other surgical procedures in the setting of ticagrelor. If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events. Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor; avoid such doses. After any initial dose, use with aspirin 75 to 100 mg/day.

Table 11. Boxed Warning for Vorapaxar[1]

WARNING
Do not use vorapaxar in patients with a history of stroke, transient ischemic attack, or intracranial hemorrhage; or active pathological bleeding. Antiplatelet agents, including vorapaxar, increase the risk of bleeding, including intracranial hemorrhage and fatal bleeding.

VII. Dosing and Administration

The usual dosing regimens for the platelet-aggregation inhibitors are listed in Table 12.

Table 12. Usual Dosing Regimens for the Platelet-Aggregation Inhibitors[1-7,13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Cilostazol	Intermittent claudication: Tablet: 100 mg orally twice daily	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg
Clopidogrel	Acute coronary syndrome, non-ST-segment elevation (unstable angina/non-Q-wave myocardial infarction): Tablet: initial, 300 mg once; maintenance, 75 mg orally once daily, administered in combination with aspirin (75 to 325 mg once daily) Acute coronary syndrome, ST-segment elevation acute myocardial infarction: Tablet: initial, 300 mg once; 75 mg once daily, administered in combination with aspirin (75 to 325 mg once daily), with or without thrombolytics; clopidogrel may be initiated with or without a loading dose Recent myocardial infarction, recent stroke, or established peripheral arterial disease: Tablet: 75 mg once daily	Safety and efficacy in children have not been established.	Tablet: 75 mg 300 mg
Prasugrel	Acute coronary syndrome: Tablet: initial, 60 mg once; maintenance, 10 mg once daily (consider 5 mg once daily for patients <60 kg), administered with aspirin (75 to 325 mg)	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Ticagrelor	Acute coronary syndrome or a history of MI: Tablet: initial, 180 mg once; maintenance, 90 mg twice daily for 12 months, then 60 mg twice daily, administered with aspirin (75 to 100 mg) Patients with CAD and No Prior Stroke or MI: Tablet: 60 mg twice daily, administered with aspirin (75 to 100 mg) Acute Ischemic Stroke or TIA:	Safety and efficacy in children have not been established.	Tablet: 60 mg 90 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 180 mg loading dose, maintenance, 90 mg twice daily for up to 30 days, administered with aspirin (75 to 100 mg)*		
Vorapaxar	Reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease: Tablet: 2.08 mg once daily in combination with aspirin and/or clopidogrel	Safety and efficacy in children have not been established.	Tablet: 2.08 mg

*After the initial loading dose of aspirin (usually 325 mg), use ticagrelor with a daily maintenance dose of aspirin 75 to 100 mg.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the platelet-aggregation inhibitors are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Platelet-Aggregation Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cerebrovascular Conditions				
Johnston et al.[33] (2020) Ticagrelor 180 mg loading dose then 90 mg twice daily maintenance + aspirin 300 to 325 mg loading dose then 75 to 100 mg once daily maintenance vs placebo + aspirin 300 to 325 mg loading dose then 75 to 100 mg once daily maintenance	DB, MC, PC, RCT Patients > 40 years of age who had mild-to-moderate acute noncardioembolic ischemic stroke or high-risk TIA	N=11,016 30 days	Primary: Composite of stroke or death Secondary: First subsequent stroke and disability measured on the Rankin scale, safety	Primary: Death or stroke occurred in 303 patients in the ticagrelor–aspirin group (5.5%) and in 362 patients in the aspirin group (6.6%) (HR, 0.83; 95% CI, 0.71 to 0.96; P=0.02). Secondary: Subsequent ischemic stroke, occurred in 276 patients in the ticagrelor–aspirin group (5.0%) and in 345 patients in the aspirin group (6.3%) (HR, 0.79; 95% CI, 0.68 to 0.93; P=0.004). Overall disability (score >1 on the modified Rankin scale) occurred in 23.8% of the patients in the ticagrelor–aspirin group and in 24.1% of the patients in the aspirin group (OR, 0.98; 95% CI, 0.89 to 1.07; P=0.61). Severe bleeding, as defined according to the GUSTO criteria (the primary safety outcome event), occurred in 28 patients (0.5%) in the ticagrelor–aspirin group and in seven patients (0.1%) in the aspirin group (HR, 3.99; 95% CI, 1.74 to 9.14; P=0.001).
Geeganage et al.[34] (2012) Dual therapy with clopidogrel or dipyridamole plus aspirin vs monotherapy with aspirin, clopidogrel	MA (12 RCTs) Patients with acute ischemic stroke or TIA	N=3,766 Duration varied	Primary: Recurrent stroke Secondary: Composite of stroke, TIA, ACS and death; composite of nonfatal stroke, nonfatal MI and vascular death; MI, severe stroke,	Primary: Dual antiplatelet therapy was associated with a significant decrease in stroke recurrence in comparison to monotherapy (3.3 vs 5.0%; RR, 0.67; 95% CI, 0.49 to 0.93). Secondary: Compared to monotherapy, dual antiplatelet therapy was associated with a significant reduction in the risk of composite endpoint of stroke, TIA, ACS and death (1.7 vs 9.1%; RR, 0.71; 95% CI, 0.56 to 0.91) as well as the composite endpoint of nonfatal stroke, nonfatal MI and vascular death (4.4 vs 6.0%; RR, 0.75; 95% CI, 0.56 to 0.99).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or dipyridamole			intracerebral hemorrhage, major bleeding, all-cause death and vascular death	No significant differences were seen between dual therapy and monotherapy with regard to the occurrence of MI (RR, 0.71; 95% CI, 0.25 to 2.03), severe stroke (RR, 1.01; 95% CI, 0.91 to 1.12), intracerebral hemorrhage (RR, 1.39; 95% CI, 0.22 to 8.75), all-cause death (RR, 1.34; 95% CI, 0.76 to 2.34) and vascular death (RR, 1.31; 95% CI, 0.59 to 2.93). Major bleeding occurred more frequently with dual therapy compared to monotherapy, though this increase was not statistically significant (RR, 2.09; 95% CI, 0.86 to 5.06).
Sacco et al.[35] (2008) PROFESS Aspirin 25 mg and dipyridamole ER 200 mg BID vs clopidogrel 75 mg QD	DB, RCT Patients ≥55 years of age with a recent ischemic stroke within 90 days of randomization	N=20,332 2.5 years	Primary: Recurrent stroke of any type Secondary: Composite of stroke, MI, or death from vascular causes	Primary: Of those in the aspirin/dipyridamole group, 916 patients (9%) experienced a recurrent stroke compared to 898 patients (8.8%) in the clopidogrel group (HR, 1.01; 95% CI, 0.92 to 1.11). Secondary: Each group had 1,333 patients (13.1%) experience MI or death from a vascular cause (HR, 0.99; 95% CI, 0.92 to 1.07).
Bath et al.[36] (2018) TARDIS Intervention group: aspirin (300 mg load then 50 to 150 mg daily, typically 75 mg), clopidogrel (300 mg load then 75 mg daily), and dipyridamole (200 mg twice daily modified release, given orally, or 100 mg three or four	Blinded-endpoint, MC, OL, RCT Patients ≥50 years of age at risk of a recurrent ischemic stroke and had either a non-cardioembolic ischemic stroke with limb weakness, dysphasia, or neuroimaging-positive hemianopia, or a non-cardioembolic TIA with at least 10 min	N=3,096 90 days	Primary: Incidence and severity (scale of 0 to 6, 0 being no symptoms and 6 being death) of recurrent stroke and TIA Secondary: Hemorrhage	Primary: The trial was stopped early on the recommendation of the data monitoring committee. The incidence and severity of recurrent stroke or TIA did not differ between intensive and guideline therapy (6% participants vs 7%; adjusted common OR, 0.90; 95% CI, 0.67 to 1.20; P=0.47). Secondary: The distribution of risk and severity of hemorrhage (using the ordinal scale of fatal, major, moderate, mild, or no hemorrhage) was shifted to more bleeding and bleeding of greater severity in participants randomly assigned to intensive antiplatelet therapy (adjusted common OR, 2.54; 95% CI, 2.05 to 3.16; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
times daily) vs guideline group: either combined aspirin and dipyridamole, or clopidogrel alone (using same doses as above) Randomly assigned antiplatelet drugs were given for 30 days after which participants were treated according to local guidelines, typically with clopidogrel alone or combined aspirin and dipyridamole	of limb weakness or isolated dysphasia			
Markus et al.[37] (2005) CARESS Clopidogrel 300 mg on day 1, followed by 75 mg QD on days 2 to7 plus aspirin 75 mg QD vs aspirin 75 mg QD	DB, PC, RCT Patients with ≥50% carotid stenosis	N=107 7 days	Primary: Proportion of patients who were MES positive on day seven Secondary: Proportion of patients who were MES positive on day two, rate of embolization on both days two and seven and their	Primary: ITT analysis revealed a significant reduction in the primary end point: 43.8% of dual-therapy patients were MES positive on day seven, as compared to 72.7% of monotherapy patients (RR reduction, 39.8%; 95% CI, 13.8 to 58.0; P=0.0046). Secondary: MES frequency per hour was reduced compared to baseline by 61.4% (95% CI, 31.6 to 78.2; P=0.0013) in the dual-therapy group at day seven and by 61.6% (95% CI, 34.9 to 77.4; P=0.0005) on day two. There were four recurrent strokes and seven TIAs in the monotherapy group vs no stroke and four TIAs in the dual-therapy group that were considered treatment emergent and ipsilateral to the qualifying carotid

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			percent change from baseline, safety	stenosis. MES frequency was greater in the 17 patients with recurrent ipsilateral events compared to the 90 without (P=0.0003).
Johnston et al.[38] (2018) POINT Clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin (at a dose of 50 to 325 mg per day) vs aspirin (at a dose of 50 to 325 mg per day) alone	MC, RCT Patients ≥18 years of age with minor ischemic stroke or high-risk TIA	N=4,881 90 days	Primary: Composite of ischemic stroke, MI, or death from ischemic vascular causes Primary safety: Risk of major hemorrhage, which was defined as symptomatic intracranial hemorrhage, intraocular bleeding causing vision loss, transfusion of ≥2 units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death due to hemorrhage Secondary: Each component of the primary efficacy outcome,	The trial was halted after 84% of the anticipated number of patients had been enrolled because the data and safety monitoring board had determined that the combination of clopidogrel and aspirin was associated with both a lower risk of major ischemic events and a higher risk of major hemorrhage than aspirin alone at 90 days. Primary: The composite primary efficacy outcome occurred in 5.0% of patients receiving clopidogrel plus aspirin and in 6.5% of patients receiving aspirin alone (HR, 0.75; 95% CI, 0.59 to 0.95; P=0.02). Primary safety: The primary safety outcome of major hemorrhage occurred in 0.9% of patients receiving clopidogrel plus aspirin and in 0.4% of patients receiving aspirin alone (HR, 2.32; 95% CI, 1.10 to 4.87; P=0.02). Secondary: The secondary outcome of ischemic stroke occurred in 4.6% of patients receiving clopidogrel plus aspirin and in 6.3% of patients receiving aspirin alone (HR, 0.72; 95% CI, 0.56 to 0.92; P=0.01). Except for stroke, there were no significant differences between treatment groups in the other components of the composite primary efficacy outcome. The risk of total ischemic or hemorrhagic stroke was lower with clopidogrel plus aspirin than with aspirin alone (HR, 0.74; 95% CI, 0.58 to 0.94; P=0.01). In analyses of secondary safety outcomes, there were no significant differences between groups in the rates of hemorrhagic stroke, symptomatic intracerebral hemorrhage, or other symptomatic intracranial hemorrhage considered separately. Death from hemorrhagic vascular causes occurred in three patients receiving clopidogrel plus aspirin and in two patients receiving aspirin alone (0.1% in each group). Nonfatal, non-intracranial hemorrhage accounted for most of the major hemorrhages. Minor hemorrhage occurred in 1.6% of patients receiving clopidogrel plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			a composite of the primary efficacy outcome and major hemorrhage, and the total number of ischemic and hemorrhagic strokes	aspirin and in 0.5% of patients receiving aspirin alone (HR, 3.12; 95% CI, 1.67 to 5.83; P=0.002).
Diener et al.[39] (2004) MATCH Clopidogrel 75 mg/day vs clopidogrel 75 mg/day and aspirin 75 mg/day	DB, PC, RCT High-risk patients with recent ischemic stroke or TIA and had at least one additional vascular risk factor who were already receiving clopidogrel	N=7,599 18 months	Primary: Composite of ischemic stroke, MI, vascular death or rehospitalization for an acute ischemic event Secondary: Death, stroke, individual components and various combinations of the primary end points	Primary: There was no significant benefit of combination therapy compared to clopidogrel monotherapy in reducing the primary outcome (15.7 vs 16.7%, respectively; P=0.244). Secondary: There was no significant benefit of combination therapy compared to clopidogrel alone in reducing the secondary outcomes. Life-threatening bleedings were higher in the group receiving aspirin and clopidogrel vs clopidogrel monotherapy (2.6 vs 1.3%; P<0.0001). Major and minor bleeding were also significantly higher with combination therapy vs clopidogrel monotherapy (P<0.0001 for both).
Wang et al.[40] (2015) CHANCE Clopidogrel-aspirin therapy (loading dose of 300 mg of clopidogrel on day one, followed by 75 mg of clopidogrel per day for 90 days, plus 75 mg of aspirin per day for the first 21	DB, PC, RCT Patients ≥40 years of age within 24 hours after onset of minor stroke or high-risk transient ischemic attack	N=5,170 1 year	Primary: Stroke event (ischemic or hemorrhagic) during 1-year follow-up Secondary: A new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial	Primary: Throughout the trial, stroke occurred in 275 patients (10.6%) in the clopidogrel-aspirin group, in comparison with 362 patients (14.0%) in the aspirin group (HR, 0.78; 95% CI, 0.65 to 0.93; P=0.006). Beyond month three, 63 (2.7%) of 2346 patients in the clopidogrel-aspirin group and 59 (2.6%) of 2260 patients in the aspirin group had a stroke (HR, 0.96; 95% CI, 0.68 to 1.35; P=0.81). Secondary: The clopidogrel-aspirin group had lower rates of combined secondary vascular events (HR, 0.78; 95% CI, 0.65 to 0.93; P=0.005) and ischemic stroke (HR, 0.77; 95% CI, 0.64 to 0.93; P=0.006) in comparison with the aspirin group. No significant difference was detected between the two

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days) vs aspirin-alone group (75 mg/d for 90 days)			infarction, or vascular death), analyzed as a composite outcome and also as individual outcomes	groups for other secondary end points. Moderate-to-severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel-aspirin group and in nine patients (0.4%) in the aspirin group (P=0.44).
Kennedy et al.[41] (2007) FASTER <u>Group 1</u> Clopidogrel 300 mg loading dose, followed by 75 mg QD vs placebo <u>Group 2</u> Simvastatin 40 mg QD vs placebo All patients were also given aspirin 81 mg QD with a 162 mg loading dose if naïve to aspirin.	DB, PC, RCT Patients ≥40 years of age with TIA or minor stroke	N=392 90 days	Primary: Incidence of stroke (ischemic and hemorrhagic), safety (hemorrhage, myositis) Secondary: Composite of stroke, MI and vascular death	Primary: The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrollment rate because of increased use of statins. Within 90 days, 7.1% of patients on clopidogrel had a stroke compared to 10.8% of patients on placebo (RR, 0.7; 95% CI, 0.3 to 1.2) for an absolute risk reduction of -3.8% (95% CI, -9.4 to 1.9; P=0.19). In the simvastatin group, 10.6% of patients had a stroke within 90 days compared to 7.3% of patients on placebo (RR, 1.3; 95% CI, 0.7 to 2.4) for an absolute risk increase of 3.3% (95% CI, -2.3 to 8.9; P=0.25). Two patients on clopidogrel had intracranial hemorrhage compared to none on placebo (absolute risk increase 1.0%; 95% CI, -0.4 to 2.4; P=0.5). There was no difference between groups for the simvastatin safety outcomes. Secondary: Clopidogrel was associated with a -3.3% risk difference in the secondary end point compared to placebo (95% CI, -9.3% to 2.7%; P=0.28). Simvastatin was associated with a 2.7% risk difference compared to placebo (95% CI, -3.2% to 8.7%; P=0.37).
Uchiyama et al.[42] (2009)	DB, RCT Japanese men 20 to	N=1,869 26 weeks and	Primary: Safety	Primary: Significantly fewer patients experienced a safety event in the clopidogrel group than the ticlopidine group (P<0.001; HR, 0.610; 95% CI 0.529,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clopidogrel 75mg QD vs ticlopidine 200 mg QD	80 years of age with a history of cerebral infarctions	52 weeks	Secondary: Combined efficacy end point of cerebral infarction, MI, and vascular death	0.703). Almost twice as many patients in the ticlopidine group (25.6%) experienced hepatic dysfunction than in the clopidogrel group (13.4%). Secondary: There was no significant difference in the incidence of the combined efficacy endpoint between clopidogrel (2.6% of patients) and ticlopidine (2.5%). Clopidogrel was better tolerated than ticlopidine; there was no difference in the efficacy of the two products with regard to the secondary prevention of vascular events in patients with prior stroke.
Johnston et al.[43] (2016) SOCRATES Ticagrelor (180 mg loading dose on day one followed by 90 mg twice daily for days two through 90) vs aspirin (300 mg on day one followed by 100 mg daily for days two through 90).	DB, DD, MC, RCT Patients with a nonsevere ischemic stroke or high-risk transient ischemic attack who had not received intravenous or intraarterial thrombolysis and were not considered to have had a cardioembolic stroke who underwent randomization within 24 hours after symptom onset	N=13,199 90 days	Primary: Time to the occurrence of stroke, myocardial infarction, or death within 90 days Secondary: Time to ischemic stroke	Primary: A primary composite end-point event occurred in 442 of the 6589 patients (6.7%) in the ticagrelor group and in 497 of the 6610 patients (7.5%) in the aspirin group (HR, 0.89; 95% CI, 0.78 to 1.01; P=0.07). Secondary: On the basis of the hierarchical testing plan, all analyses of secondary end points were therefore considered to be exploratory and were not used to make conclusions regarding significance. The main secondary end point, ischemic stroke, occurred in 385 patients (5.8%) in the ticagrelor group and 441 patients (6.7%) in the aspirin group (HR, 0.87; 95% CI, 0.76 to 1.00; nominal P=0.046).
Fukuuchi et al.[44] (2008) Ticlopidine 200 mg QD vs	DB, DD, MC, RCT Japanese patients between the ages of 20 and 80 years who experienced a non-cardioembolic	N=1,151 52 weeks	Primary: Safety with emphasis on hematologic changes, hepatic dysfunction, nontraumatic	Primary: During the 52-week study period, 15.1% of ticlopidine patients and 7.0% of clopidogrel patients had at least one primary safety end point (P<0.001). Significant differences were primarily noted between ticlopidine and clopidogrel for hematologic disorders (2.4 vs 1.0%; P=0.043) and hepatic dysfunction (11.9 vs 4.2%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clopidogrel 75 mg QD	cerebral infarction ≥8 days prior to enrollment		hemorrhage and other serious adverse reactions Secondary: Combined incidence of nonfatal or fatal cerebral infarction or MI, or death due to other vascular causes	Study medication was discontinued prematurely due to safety end points in 27 and 17% of patients receiving ticlopidine and clopidogrel, respectively (P<0.001). The HR for the risk of discontinuing study medication due to a primary safety end point was 0.559 (95% CI, 0.434 to 0.721) in favor of clopidogrel. Secondary: The incidence of vascular events did not differ significantly between ticlopidine and clopidogrel (2.6 vs 3.0%, respectively; P=0.948; HR, 0.977; 95% CI, 0.448 to 1.957).
Gent et al.[45] (1989) CATS Ticlopidine 250 mg BID vs placebo	DB, MC, PC, RCT Patients with ischemic strokes occurring from one week to four months	N=1,072 Up to 3 years	Primary: Event rate per year for stroke, MI, or vascular death Secondary: Adverse events	Primary: The event rate per year for stroke, MI or vascular death was 10.8% in the ticlopidine group and 15.3% in the placebo group. Compared to placebo, ticlopidine reduced the RR of stroke, MI or vascular death by 30% (P=0.006) in the on-treatment analysis and by 23% (P=0.020) using the intent-to-treat approach. Ticlopidine reduced the RR of ischemic stroke by 33% (P=0.008) in the on-treatment analysis. Ticlopidine was beneficial for both men and women (RR, 28.1%; P=0.037 and RR, 34.2%; P=0.045, respectively). Secondary: Adverse events associated with ticlopidine included neutropenia (severe in about 1% of cases), skin rash (severe 2%) and diarrhea (severe 2%).
Hass et al.[46] (1989) TASS Ticlopidine 250 mg BID vs	Blinded, MC, RCT Patients with recent (within three months) minor stroke or TIA	N=3,069 2 to 6 years	Primary: Nonfatal stroke or death Secondary: Adverse events	Primary: Compared to aspirin, ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate was 17% for ticlopidine vs 19% for aspirin; P=0.048). Ticlopidine reduced the risk of stroke after three years by 21% (10% for ticlopidine vs 13% for aspirin; P=0.024). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin 650 mg BID				Ticlopidine significantly increased total cholesterol compared to aspirin (9 vs 2%; P<0.01). Serious gastrointestinal adverse effects were 2.5 times more common in the aspirin group but bleeding from other anatomic sites was infrequent and about equal in the two treatment groups. Severe neutropenia occurred in 0.9% of patients.
Gorelick et al.[47] (2003) AAASPS Ticlopidine 250 mg BID vs aspirin 325 mg BID	DB, MC, RCT African American men and women who recently had a non-cardioembolic ischemic stroke	N=1,809 Up to 2 years	Primary: Composite of recurrent stroke, MI, or vascular death Secondary: Fatal or nonfatal stroke	Primary: There was no statistically significant difference in the percent of patients reaching the primary outcome of recurrent stroke, MI or vascular death between ticlopidine and aspirin (14.7 vs 12.3%, respectively; P=0.12). Secondary: There was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group (P=0.08). The frequency of laboratory-determined serious neutropenia was 3.4% for ticlopidine vs 2.2% for aspirin (P=0.12).
Combined Cardiovascular and Cerebrovascular Conditions				
Antithrombotic Trialists' Collaboration.[48] (2002) Antiplatelet agents vs control vs one antiplatelet regimen vs another	MA (287 trials) Patients at high risk of occlusive vascular events	N=135,640 Duration varied	Primary: "Serious vascular event" (nonfatal MI, nonfatal stroke or vascular death) Secondary: Not reported	Primary: Overall, antiplatelet therapy reduced the combined outcome of any serious vascular event by 25%, nonfatal MI by 34%, nonfatal stroke by 25%, and vascular mortality by 15% with no apparent adverse effect on other deaths. Aspirin was the most widely studied antiplatelet drug and low dose (75 to 150 mg daily) was at least as effective as higher daily doses for long-term use. In acute settings an initial loading dose of at least 150 mg aspirin may be required. Clopidogrel reduced serious vascular event by 10% compared to aspirin, which was similar to the 12% reduction observed with ticlopidine. The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared to aspirin alone. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Sudlow et al.[49] (2009) Aspirin (325 mg/day for most studies) vs clopidogrel (75 mg QD for most studies) or ticlopidine (250 mg BID for most studies)	MA (10 trials) Patients at high risk for serious vascular events, including those with a previous TIA or ischemic stroke	N=26,865 Duration varied	Primary: Composite outcome of stroke, MI, or death from a vascular cause Secondary: Outcomes of adverse drug events	Primary: Treatment with clopidogrel or ticlopidine produced a modest reduction in the odds of a serious vascular event (11.6%) vs aspirin (12.5%; OR, 0.92; 95% CI, 0.85 to 0.99). This corresponds to the avoidance of 10 serious vascular events per 1,000 patients treated with clopidogrel or ticlopidine rather than aspirin for an average of about two years. Secondary: Compared to aspirin, clopidogrel and ticlopidine significantly reduced gastrointestinal adverse effects. However, clopidogrel and ticlopidine increased the odds of skin rash and diarrhea, *ticlopidine* more than clopidogrel. Allocation to *ticlopidine*, but not clopidogrel, significantly increased the odds of neutropenia.
CAPRIE Steering Committee[50] (1996) CAPRIE Clopidogrel 75 mg QD vs aspirin 325 QD	DB, MC, PG, RCT Patients with recent ischemic stroke (within six months with at least a week of residual neurological signs), recent MI (within 35 days) or symptomatic peripheral arterial disease	N=19,185 1 to 3 years	Primary: Composite outcome of ischemic stroke, MI or vascular death Secondary: Primary outcome and amputation, vascular death, all-cause mortality, safety	Primary: Intention–to-treat analysis showed that patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, MI, or vascular death compared to 5.83% with aspirin, for a RR reduction of 8.7% (95% CI, 0.3 to 16.5; P=0.043) in favor of clopidogrel. Corresponding on-treatment analysis yielded a RR reduction of 9.4% in favor of clopidogrel. For the 6,431 patients admitted to the study with prior stroke, the RR reduction for ischemic stroke, MI, or vascular death was 7.3% in favor of clopidogrel (P=0.26), and the RR reduction for the end point of stroke was 8.0% (P=0.28). For the 6,302 patients admitted to the study with myocardial infarction, an RR increase of 3.7% was associated with clopidogrel (P=0.66). For the 6,452 patients admitted to the study with peripheral arterial disease, an RR of 23.8% was noted in favor of clopidogrel (P=0.0028). Secondary: Clopidogrel reduced the risk of the primary outcome plus amputation by 7.6% compared to aspirin (P=0.076).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference between clopidogrel and aspirin with regards to vascular death (1.90 vs 2.06%; P=0.29) and all-cause mortality (3.05 vs 3.11%; P=0.71). There were no major differences in terms of safety. Severe rash (P=0.017) and severe diarrhea (P=0.080) were reported more frequently with clopidogrel and severe upper gastrointestinal discomfort (P=0.096), intracranial hemorrhage (P=0.23) and gastrointestinal hemorrhage (P=0.05) were reported more frequently with aspirin.
Zhou et al.[51] (2012) Aspirin plus clopidogrel vs aspirin vs clopidogrel	MA, SR (7 RCTs) Trials evaluating the use of aspirin and/or clopidogrel patients for primary and/or secondary prevention	N=48,248 Duration varied	Primary: Major cardiovascular events Secondary: Not reported	Primary: Overall, with combination therapy the harm of major cardiovascular events was significantly reduced by 9% (RR, 0.91; 95% CI, 0.83 to 0.98) compared to monotherapy with aspirin and clopidogrel (six trials; n=46,132). Combination therapy resulted in a significant 14% reduction in the harm of MI compared to monotherapy with aspirin and clopidogrel (RR, 0.86; 95% CI, 0.76 to 0.97) (seven trials; n=48,248). Combination therapy resulted in a significant 16% reduction in the harm of stroke compared to monotherapy with aspirin and clopidogrel (RR, 0.84; 95% CI, 0.72 to 0.99) (seven trials; n=48,248). There was no evidence to show that combination therapy could reduce the risk of mortality, regardless of total mortality, vascular death, or non-vascular death compared to monotherapy aspirin and clopidogrel. There was no effect of combination therapy on the harm of revascularization events compared to monotherapy with aspirin and clopidogrel. Combination therapy significantly increased the harm of major bleeding events by 62% compared to monotherapy with aspirin and clopidogrel (RR, 1.62; 95% CI, 1.26 to 2.08) (seven trials; n=46,073). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
DeSchryver et al.[52] (2007) Dipyridamole with or without other antiplatelet drugs vs control (no drug or another antiplatelet drug)	MA (29 trials) Patients with arterial vascular disease (angina, CAD, MI, nephropathy, PAD, retinopathy, stroke and TIA)	N=23,019 Duration varied	Primary: Secondary prevention of vascular death and vascular events (defined as vascular death or any death from an unknown cause, nonfatal stroke or nonfatal MI) Secondary: Not reported	Primary: Compared to control, dipyridamole had no clear effect on vascular death (RR, 0.99; 95% CI, 0.87 to 1.12). The dose of dipyridamole or type of presenting vascular disease did not influence this result. Compared to control, dipyridamole appeared to reduce the risk of vascular events (RR, 0.88; 95% CI, 0.81 to 0.95). This effect was only statistically significant in patients presenting with cerebral ischemia. There was no evidence that dipyridamole alone was more efficacious than aspirin. Secondary: Not reported
Cardiovascular Conditions (Acute Coronary Syndrome, Myocardial Infarction, Angina Pectoris)				
CURE Trial Investigators[53] (2001) CURE Clopidogrel (300 mg immediately, followed by 75 mg QD) plus aspirin vs aspirin	DB, PC, RCT Patients with NSTEMI, presenting within 24 hours of symptom onset	N=12,562 3 to 12 months	Primary: Composite of death from cardiovascular causes, nonfatal MI, or stroke (first primary outcome); composite of the first primary outcome or refractory ischemia (second primary outcome) Secondary: Severe ischemia, heart failure, need for revascularization, safety	Primary: A composite of death from cardiovascular causes, nonfatal MI, or stroke occurred in 9.3% of patients in the clopidogrel and aspirin group compared to 11.4% of patients in the aspirin group (RR, 0.80; 95% CI, 0.72 to 0.90; P<0.001). When refractory ischemia was included with the first primary outcome, the composite rate was 16.5% in the clopidogrel and aspirin group compared to 18.8% for aspirin alone (RR, 0.86; 95% CI, 0.79 to 0.94; P<0.001). Secondary: Significant reductions in nonfatal MI (5.2 vs 6.7%) and trends toward reduction in death (5.1 vs 5.5%) and stroke (1.2 vs 1.4%) with clopidogrel plus aspirin vs aspirin alone were noted. The percentages of patients with in hospital refractory or severe ischemia, recurrent angina, heart failure and revascularization procedures were also significantly lower with clopidogrel plus aspirin vs aspirin alone (P<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were significantly more patients with major bleeding in the clopidogrel plus aspirin group than in the aspirin group (3.7 vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; P=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.1 vs 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56; P=0.13).
COMMIT Collaborative Group[54] (2005) COMMIT Clopidogrel 75 mg/day plus aspirin 162 mg/day vs aspirin 162 mg/day	MC, PC, RCT Patients admitted to the hospital within 24 hours of suspected acute MI, mean age 61 years	N=45,852 15 days (mean duration)	Primary: Composite of death, reinfarction or stroke; death from any cause Secondary: Safety	Primary: Allocation to clopidogrel plus aspirin produced a highly significant 9% proportional reduction in death, reinfarction or stroke compared to aspirin alone (actual reductions 9.2 vs 10.1%, respectively; P=0.002), corresponding to nine fewer events per 1,000 patients treated for about two weeks. There was also a significant 7% proportional reduction in any death in the clopidogrel plus aspirin group compared to aspirin alone (7.5 vs 8.1%; P=0.03). Secondary: Considering all fatal, transfused, or cerebral bleeds together, no significant excess risk was noted with clopidogrel plus aspirin vs aspirin alone, either overall (0.58 vs 0.55%, respectively; P=0.59) or in patients older than 70 years or in those given fibrinolytic therapy.
Sabatine et al.[55] (2005) CLARITY-TIMI 28 Clopidogrel 300 mg loading dose, followed by 75 mg QD plus aspirin vs aspirin Patients received a fibrinolytic agent, and heparin when	DB, MC, PC, RCT Patients 18 to 75 years of age who presented within 12 hours after the onset of a STEMI	N=3,491 30 days	Primary: Composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography (death or recurrent MI by day 8 or hospital discharge in patients who did not undergo angiography) Secondary:	Primary: The primary end point was reached in 15.0% of patients receiving clopidogrel vs 21.7% for placebo, representing an absolute reduction of 6.7% in the rate and 36% in the odds of reaching the end point with clopidogrel therapy (95% CI, 27 to 47; P<0.001). By 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20% (from 14.1 to 11.6%; P=0.03). Secondary: The rates of major bleeding and intracranial hemorrhage were similar in the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
appropriate.			Safety	
Ahmed et al.[56] (2011) Clopidogrel 300 mg once, followed by 75 mg/day vs placebo Patients received a fibrinolytic agent, aspirin, and when appropriate, heparin.	Substudy of CLARITY-TIMI 28 trial Patients 18 to 75 years of age who presented within 12 hours after the onset of a STEMI stratified by baseline GFR	N=3,252 30 days (study medication given up to, and including, the day of angiography, or up to day 8 or hospital discharge if no angiography)	Primary: Composite of an occluded infarct-related artery on angiography, all-cause mortality or recurrent MI prior to angiography (death or recurrent MI by day eight or hospital discharge in patients who did not undergo angiography) Secondary: Composite clinical endpoint of cardiovascular death, MI, or recurrent ischemia leading to urgent revascularization at 30 days; cardiovascular death; safety	Primary: There was a significant trend for an increased rate of the primary composite endpoint with lower GFR and was the highest rate (23.4%) in patients with moderately reduced GFR (P=0.003). Secondary: By day 30, both the rates of the composite clinical endpoint (P<0.0001) and the safety endpoints of bleeding (P=0.0008) and intracranial hemorrhage (P=0.03) also trended towards a significant increase with lower GFRs. By day 30, there was a significant trend for an increased rate of cardiovascular death with lower GFR and was the highest rate (11.3%) in patients with moderately reduced GFR (P<0.0001).
Bhatt et al.[57] (2006) CHARISMA Clopidogrel 75 mg QD plus aspirin 75 to 162 mg QD vs	DB, MC, PC, RCT Patients 45 years of age or older with clinically evident cardiovascular disease (e.g., documented coronary, cerebrovascular or	N=15,603 28 months	Primary: Composite of first occurrence of MI, stroke, or death from cardiovascular causes Secondary: First occurrence of	Primary: The composite of MI, stroke or death from cardiovascular causes was 6.8% with clopidogrel plus aspirin and 7.3% with aspirin (RR, 0.93; 95% CI, 0.83 to 1.05; P=0.22). The rate of the primary end point among patients with multiple risk factors was 6.6% with clopidogrel plus aspirin and 5.5% with aspirin alone (RR, 1.2; 95% CI, 0.91 to 1.59; P=0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel plus aspirin than aspirin alone (3.9 vs 2.2%; P=0.01). In the subgroup with clinically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin 75 to 162 mg QD	peripheral arterial disease) or multiple atherothrombotic risk factors		MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	evident atherothrombosis, the rate was 6.9% with clopidogrel plus aspirin and 7.9% with aspirin alone (RR, 0.88; 95% CI, 0.77 to 1.00; P=0.046). Secondary: The secondary end point was reached in 16.7 and 17.9% (RR, 0.92; 95% CI, 0.86 to 1.00; P=0.04) of patients receiving clopidogrel plus aspirin vs aspirin alone, respectively. The rate of severe bleeding was 1.7 and 1.3% (RR, 1.25; 95% CI, 0.97 to 1.61; P=0.09) for patients receiving clopidogrel plus aspirin vs aspirin.
Dasgupta et al.[58] (2009) Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day vs aspirin 75 to 162 mg/day	Post hoc analysis of CHARISMA Post hoc analysis of patients with diabetic neuropathy in the CHARISMA trial, who were ≥45 years of age with clinically evident cardiovascular disease or multiple atherothrombotic risk factors	N=2,009 Median 28 months	Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes Secondary: First occurrence of MI, stroke, death from cardiovascular causes or hospitalization for unstable angina, TIA or revascularization procedure; safety	Primary: Almost all cardiovascular events occurred significantly more frequently in diabetic patients with neuropathy. Patients with diabetic neuropathy had a higher case fatality rate of MI compared to diabetic patients without nephropathy and nondiabetic patients (20 vs 14 vs 11%, respectively), but this higher rate was not significant (P=0.240). Secondary: Patients with nephropathy who were assigned clopidogrel experienced a significant increase in overall mortality (HR, 1.8; 95% CI, 1.2 to 2.7; P=0.006) compared to placebo, as well as significantly increased cardiovascular mortality (HR, 1.7; 95% CI, 1.1 to 2.9; P=0.028). The frequency of bleeding in patients with diabetic nephropathy who received clopidogrel tended to be higher compared to placebo, but this increase was not significant (2.6 vs 1.5%; HR, 1.8; P=0.075).
Hart et al.[59] (2008) CHARISMA Clopidogrel 75 mg QD plus aspirin 75 to 162 mg QD	DB, MC, PC, RCT (Post hoc analysis of participants with a history of atrial fibrillation in the CHARISMA trial) Patients 45 years of	N=593 28 months (median duration)	Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes	Primary: There was no difference in the composite of stroke, MI or vascular death between patients receiving clopidogrel plus aspirin (35 of 298 patients) and aspirin alone (27 of 285 patients; P=0.40). Secondary: There was no difference in the composite of stroke, MI, vascular death or rehospitalization (70 vs 66 patients; P=0.93) or all-cause mortality (29 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 75 to 162 mg QD	age or older with clinically evident cardiovascular disease or multiple atherothrombotic risk factors; patients receiving oral anticoagulation were excluded		Secondary: First occurrence of MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	25 patients; P=0.69) among patients receiving clopidogrel plus aspirin and aspirin alone. Stroke (ischemic and hemorrhagic) occurred in 15 patients receiving clopidogrel plus aspirin (2.2% per year) and in 14 patients receiving aspirin alone (2.1% per year; HR, 1.03; 95% CI, 0.49 to 2.13; P=0.94). Severe or fatal extracranial hemorrhage occurred in six patients given clopidogrel plus aspirin vs three patients given aspirin alone (P=0.51), while intracranial bleeding occurred in three patients vs one patient (P=0.62), respectively.
Ho et al.[60] (2008) Clopidogrel (dose not specified)	RETRO Patients with ACS discharged on clopidogrel from Veterans Affairs hospitals	N=3,137 Duration varied	Primary: Rate of all-cause mortality or acute MI after stopping clopidogrel Secondary: Not reported	Primary: Among medically treated patients, mean duration of clopidogrel treatment was 302 days. Death or acute MI occurred in 17.1% of patients, with 60.8% of events occurring during 0 to 90 days, 21.3% during 91 to 180 days, and 9.7% during 181 to 270 days after stopping treatment with clopidogrel. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping treatment with clopidogrel was associated with a significantly higher risk of adverse events (IRR, 1.98; 95% CI, 1.46 to 2.69 vs the interval 91-180 days). Among the PCI-treated patients with ACS, mean duration of clopidogrel treatment was 278 days and death or acute MI occurred in 7.9% of patients, with 58.9% of events occurring during 0 to 90 days, 23.4% during 91 to 180 days, and 6.5% during 181 to 270 days after stopping clopidogrel treatment. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping clopidogrel treatment was associated with a significantly higher risk of adverse events (IRR, 1.82; 95% CI, 1.17 to 2.83). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wiviott et al.[61] (2007) TRITON-TIMI 38 Clopidogrel 300 mg loading dose followed by 75mg daily plus aspirin 75 to 162 mg/daily vs prasugrel 60 mg loading dose followed by 10 mg daily plus aspirin 75 to 162 mg/daily	AC, DB, MC, RCT Patients with moderate-to-high risk ACS (unstable angina, NSTEMI, or STEMI) and scheduled PCI	N=13,608 Mean 14.5 months	Primary: Composite of death from CV causes, nonfatal MI, or nonfatal stroke Secondary: Stent thrombosis, composite of CV death, nonfatal MI, nonfatal stroke, or rehospitalization due to cardiac ischemic event, 30 and 90 day event rates for the primary endpoint and composite of CV death, nonfatal MI, or urgent target vessel revascularization	Primary: Compared to clopidogrel, treatment with prasugrel was associated with a reduction in the composite primary efficacy endpoint of death from CV causes, nonfatal MI, or nonfatal stroke (9.9 vs 12.1%, respectively; HR, 0.81; 95% CI, 0.73 to 0.9; P<0.001). This difference was driven primarily by a reduction in nonfatal MI, which was evident early on in therapy. Secondary: In a post-hoc analysis, probable or definite stent thrombosis was also significantly reduced in the prasugrel vs clopidogrel group (1.1 vs 2.4%; HR, 0.48; 95% CI 0.36 to 0.64; P<0.001), a finding that was observed with both bare metal and drug eluding stents. The composite of CV death, nonfatal MI, nonfatal stroke, and re-hospitalization for ischemia was 12.3% for prasugrel compared to 14.6% for clopidogrel (HR, 0.78; 95% CI, 0.69 to 0.89). The improvement in efficacy outcomes with prasugrel was accompanied by an increased risk of bleeding compared to clopidogrel. A higher percentage of patients treated with prasugrel had major bleeding than those treated with clopidogrel (2.4 vs 1.8%; P=0.03). There was a significant increase in life-threatening bleeding with prasugrel and a significant increase in fatal bleeding (0.4 vs 0.1%; P=0.002) compared to clopidogrel.
Wiviott et al.[62] (2008) Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75	Subanalysis of TRITON-TIMI 38 TRITON-TIMI 38 patients with a median age of 63 stratified by diabetes	N=13,608 (n=3,146 diabetes population) 6 to 15 months (median, 14.5 months)	Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke Secondary: Rate of cardiovascular	Primary: The composite endpoint in patients with diabetes was significantly lower in the prasugrel group (12.2%) than in the clopidogrel group (17.0%; HR, 0.70; 95% CI, 0.58 to 0.85; P<0.001). A 14.0% overall reduction in the primary endpoint was seen in the prasugrel and no diabetes group compared to the clopidogrel group (HR, 0.86; 95% CI, 0.76 to 0.98; P=0.02). Among the diabetes group the reduction was 30% in the prasugrel group compared to the clopidogrel group (HR, 0.70; 95% CI, 0.58 to 0.85;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).			death, MI (fatal or nonfatal) or stent thrombosis; safety; net clinical benefit	P<0.001). Secondary: The rate of cardiovascular death in patients with diabetes was not significantly lower in the prasugrel group (3.4%) than in the clopidogrel group (4.2%; HR, 0.85; 95% CI, 0.58 to 1.24; P=0.40). The rate of MI in patients with diabetes was significantly lower in the prasugrel group (8.2%) than in the clopidogrel group (13.2%; HR, 0.60; 95% CI, 0.48 to 0.76; P<0.001). The rate of MI in patients without diabetes was also significantly lower in the prasugrel group (8.7%) than in the clopidogrel group (7.2%; HR, 0.82; 95% CI, 0.72 to 0.95; P=0.006). There was an 18.0% reduction in MI among nondiabetic prasugrel patients compared to a 40.0% reduction in MI among diabetic prasugrel patients. The rate of stent thrombosis in patients with diabetes was significantly lower in the prasugrel group (2.0%) than in the clopidogrel group (3.6%; HR, 0.52; 95% CI, 0.33 to 0.84; P=0.007). The rate of TIMI major non-CABG bleeding in patients with diabetes was not significantly greater in the prasugrel group (2.5%) compared to the clopidogrel group (2.6%; HR, 1.06; 95% CI, 0.66 to 1.69; P=0.81). The rate of TIMI major or minor non-CABG bleeding in patients with diabetes was not significantly greater in the prasugrel group (5.3%) compared to the clopidogrel group (4.3%; HR, 1.30; 95% CI, 0.92 to 1.82; P=0.13). The rate of net clinical benefit was significantly greater in the prasugrel group (14.6%) than in the clopidogrel group (19.2%; HR, 0.74; 95% CI, 0.62 to 0.89; P=0.001).
Antman et al.[63] (2008) Prasugrel 60 mg once, followed by 10 mg/day	Subanalysis of TRITON-TIMI 38 Patients with ACS (unstable angina, NSTEMI or STEMI)	N=13,608 6 to 15 months (median, 14.5 months)	Primary: Rate of MI, stent thrombosis and urgent target vessel revascularization from	Primary: The rate of MI was significantly lower in the prasugrel group (4.27%) than in the clopidogrel group by day three (5.24%; HR, 0.81; 95% CI, 0.70 to 0.95; P=0.008) and from day three until the end of the study (3.40 vs 4.79%; HR, 0.69; 95% CI, 0.58 to 0.83; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	with a scheduled PCI; for patients with unstable angina or NSTEMI ischemic symptoms lasting ≥10 minutes and occurring within 72 hours of randomization, a TIMI score ≥3 and either ST-segment deviation ≥1 mm or elevated cardiac necrosis biomarker levels; STEMI patients were included within 12 hours after symptom onset if PCI was planned or within 14 days after receiving medical treatment for STEMI		randomization to day three and from day three to the end of the trial Secondary: Safety, percent net clinical benefit	The rate of stent thrombosis was significantly lower in the prasugrel group than in the clopidogrel group by day three (0.33 vs 0.67%; HR, 0.49; 95% CI, 0.29 to 0.82; P=0.006) and from day three until the end of the study (0.08 vs 1.74%; HR, 0.45; 95% CI, 0.32 to 0.64; P<0.0001). The rate of urgent target vessel revascularization was significantly lower in the prasugrel group than in the clopidogrel group by day three (0.54 vs 0.83%; HR, 0.66; 95% CI, 0.43 to 0.99; P=0.047) and from day three until the end of the study (1.94 vs 2.97%; HR, 0.65; 95% CI, 0.52 to 0.82; P=0.0003). Secondary: Through the first three days the rate of TIMI major non-CABG bleeding was numerically greater in the prasugrel group (0.74%) compared to the clopidogrel group (0.61%), however the difference between the two groups was not significant, (P=0.35). From day three to the end of the trial prasugrel was associated with a significantly greater risk of TIMI major non-CABG bleeding (1.71%) compared to clopidogrel (1.23%; HR, 1.39; 95% CI, 1.02 to 1.89; P=0.036). The rate of net clinical benefit was significantly greater in the prasugrel group than in the clopidogrel group by day three (6.19 vs 5.29%; HR, 0.85; 95% CI, 0.74 to 0.98; P=0.025) and from day three until the end of the study (8.33 vs 7.35%; HR, 0.87; 95% CI, 0.77 to 0.98; P=0.028).
Murphy et al.[64] (2008) Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75	Subanalysis of TRITON-TIMI 38 Patients with ACS (unstable angina, NSTEMI or STEMI) with a scheduled PCI; for patients with unstable angina or NSTEMI ischemic symptoms	N=13,608 6 to 15 months (median, 14.5 months)	Primary: Total number of reoccurrences of the composite endpoint (rate of death from cardiovascular causes, nonfatal MI or nonfatal stroke), risk of second event	Primary: Prasugrel demonstrated a significant overall reduction in subsequent events with 195 fewer total primary events compared to clopidogrel (HR, 0.79; 95% CI, 0.71 to 0.87; P<0.001). From the time of the first event to the recurrent event or last follow up a second event occurred in 10.8% of the prasugrel group compared to 15.4% in the clopidogrel group (HR, 0.65; 95% CI, 0.46 to 0.92; P=0.016). Cardiovascular death following the nonfatal event was also reduced in the prasugrel group (3.7%) compared to the clopidogrel group (7.1%; HR,

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mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	lasting ≥10 minutes and occurring within 72 hours of randomization, a TIMI score ≥3 and either ST-segment deviation ≥1 mm or elevated cardiac necrosis biomarker levels; STEMI patients were included within 12 hours after symptom onset if PCI was planned or within 14 days after receiving medical treatment for STEMI		following initial event, cardiovascular deaths following nonfatal event Secondary: Safety	0.46; 95% CI, 0.25 to 0.82; P=0.008). Secondary: Recurrent bleeding events occurred infrequently, with TIMI major non-CABG bleeds in four patients treated with prasugrel and two with clopidogrel. There were also five repeat TIMI minor non-CABG bleeds in each treatment group. Among patients with at least one TIMI non-CABG major or minor bleeding event, 17 were reported in the prasugrel group and 13 were reported in the clopidogrel group.
Montalescot et al.[65] (2009) Clopidogrel 300 mg loading dose followed by 75mg daily plus aspirin 75 to 162 mg/daily vs prasugrel 60 mg loading dose followed by 10 mg daily plus aspirin 75 to 162 mg/daily	Subanalysis of TRITON-TIMI 38 Patients who presented within 12 hours of onset of symptoms of STEMI for whom primary PCI was planned	N=3,534 (Subgroup analysis of STEMI patients) 15 months	Primary: Composite of CV death, non-fatal MI, or non-fatal stroke Secondary: CV death, non-fatal MI, or urgent target vessel revascularization at 30 days	Primary: At 30 days, 115 (9.5%) individuals assigned prasugrel group had met the primary endpoint compared to 166 (9.5%) allocated to the clopidogrel group (HR, 0.68 [95% CI 0.54 to 0.87]; P=0.0017). This effect continued to 15 months (174 [10·0%] vs 216 [12·4%]; 0.79 [0.65 to 0.97]; P=0.0221). Secondary: At 30 days, the secondary endpoints of CV death, MI, or urgent target vessel revascularization were significantly reduced with prasugrel (HR, 0.75; 95% CI, 0.59 to 0.96; P=0.0205) and 15 months (HR, 0.79; 0.65 to 0.97; P=0.0250), as was stent thrombosis.
Pride et al.[66] (2009)	Subanalysis of TRITON-TIMI 38	N=13,608 (n=569 PCI population)	Primary: Composite of death from	Primary: The primary endpoint occurred in 14.2% of patients randomized to prasugrel and 17.1% of patients randomized to clopidogrel, a

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Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	TRITON-TIMI 38 patients who underwent PCI without stent implantation	6 to 15 months (median, 14.5 months)	cardiovascular causes, nonfatal MI or nonfatal stroke Secondary: Composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke or urgent target vessel revascularization; safety	nonsignificant 18.0% RR reduction (HR, 0.82; 95% CI, 0.53 to 1.25; P=0.27). Overall, the unadjusted incidence of the primary composite outcome was significantly higher among patients who underwent PCI without stent implantation compared to those who received stents (15.6 vs 10.8%; P=0.001). Secondary: There were significant reductions in the incidence of urgent target vessel revascularization (3.6 vs 8.2%; HR, 0.46; 95% CI, 0.22 to 0.98; P=0.040), any target vessel revascularization (4.0 vs 10.1%; HR, 0.40; 95% CI, 0.20 to 0.82; P=0.009), the composite of any revascularization procedure (6.3 vs 12.9%; HR, 0.48; 95% CI, 0.27 to 0.87; P=0.014), and CABG surgery (12.5 vs 19.4%; HR, 0.62; 95% CI, 0.40 to 0.98; P=0.041) with prasugrel compared to clopidogrel. There were trends towards reductions in nonfatal MI (9.1 vs 13.5%; HR, 0.65; 95% CI, 0.39 to 1.10; P=0.11) and all MI (9.8 vs 13.9%; HR, 0.69; 95% CI, 0.41 to 1.14; P=0.14) favoring prasugrel. The incidence of all cause mortality, cardiovascular death and nonfatal and all stroke did not differ significantly between the groups. Non-CABG-related major bleeding was more frequent among patients randomized to prasugrel (2.1 vs 0.0%; P=0.033), and there was a trend toward an increased incidence of non-CABG-related life-threatening bleeding (1.7 vs 0.0%; P=0.057). The incidence of intracranial hemorrhage and the composite of non-CABG TIMI major and minor bleeding did not differ significantly between the groups (4.3 vs 2.2%; HR, 1.85; 95% CI, 0.63 to 5.42), although there was no significant interactions between bleeding rates and treatment with prasugrel compared to clopidogrel as a function of PCI stent (stent vs no stent).
O'Donoghue et al.[67] (2009) Prasugrel 60 mg once, followed by 10	Subanalysis of TRITON-TIMI 38 TRITON-TIMI 38 patients stratified by	N=13,608 (n=7,414 GP IIb/IIIa inhibitor population)	Primary: Composite of death from cardiovascular causes, nonfatal	Primary: There was a consistent benefit of prasugrel over clopidogrel in reducing cardiovascular death, MI or stroke at 30 days in patients who did (HR, 0.76; 95% CI, 0.64 to 0.90) and did not (HR, 0.78; 95% CI, 0.63 to 0.97; P=0.83) receive a GP IIb/IIIa inhibitor.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	GB IIb/IIIa inhibitor use	30 days	MI or nonfatal stroke Secondary: Periprocedural MI, urgent target vessel revascularization, stent thrombosis, safety	Secondary: Prasugrel significantly reduced the risk of recurrent MI in subjects by approximately 25% regardless of the use of a GP IIb/IIIa inhibitor, including a comparable benefit toward a reduction in periprocedural MI across both subgroups. Patients treated with prasugrel also exhibited a significant reduction in urgent target vessel revascularization, irrespective of whether or not they were treated with a GP IIb/IIIa inhibitor (P=0.63). At the end of 30 days, prasugrel significantly reduced the risk of stent thrombosis by 54% in patients treated with a GP IIb/IIIa inhibitor (HR, 0.46; 95% CI, 0.29 to 0.71) and by 66% in patients not treated with a GP IIb/IIIa inhibitor (HR, 0.34; 95% CI, 0.17 to 0.65; P=0.46). In the overall cohort, prasugrel significantly increased the risk of TIMI non-CABG-related major or minor bleeding compared to clopidogrel (2.6 vs 2.1; HR, 1.26; 95% CI, 1.01 to 1.57; P=0.04). The excess risk of TIMI non-CABG-related major or minor bleeding observed with prasugrel was comparable regardless of whether a GP IIb/IIIa inhibitor was used (HR, 1.16; 95% CI, 0.89 to 1.50) or was not used (HR, 1.63; 95% CI, 1.05 to 2.52; P=0.19). The absolute excess in the risk of TIMI non-CABG-related major bleeding with prasugrel vs clopidogrel was 0.1% in patients treated with a GP IIb/IIIa inhibitor (1.2 vs 1.1%; HR, 1.06; 95% CI, 0.69 to 1.64) and 0.3% in subjects not treated with a GP IIb/IIIa inhibitor (0.9 vs 0.6%; HR, 1.47; 95% CI, 0.81 to 2.66), a difference that was not significantly different between subgroups (P=0.39). Similarly, the relative hazard of TIMI life-threatening bleeding with prasugrel compared to clopidogrel did not differ significantly in the presence or absence of a GP IIb/IIIa inhibitor (P=0.19). The incidence of procedure-related TIMI major bleeding was similar for subjects treated with prasugrel or clopidogrel and was not significantly influenced by the use of a GP IIb/IIIa inhibitor (P value not reported). Consistent with the overall trial, there was no significant difference in the incidence of intracranial hemorrhage between treatment arms in either stratum (P value not reported).
Zeymer et al.[68]	OBS, PRO	N=3,291	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2015) Clopidogrel vs prasugrel	Patients with STEMI of less than 24 hour duration undergoing angiography and treated with a loading dose of either clopidogrel or prasugrel	median of six days after start of treatment	Major adverse cardiac and cerebral events (MACCE), defined as death, non-fatal infarction and non-fatal stroke; major bleeding Secondary: Not reported	Prasugrel was predominantly used in patients <75 years, body weight >60 kg and those without prior stroke. In-hospital mortality was numerically lower in the prasugrel group (1.7 vs 4.4%), as well as non-fatal reinfarction (0.2 vs 0.5%), non-fatal stroke (0.1 vs 0.3%) and MACCE (2.1 vs 5.2%), while there was no difference in major bleeding complications (0.8 vs 0.9%). In the multivariate analysis the MACCE-rate tended to be lower in prasugrel treated patients (odds ratio 0.71, 95% CI, 0.42 to 1.08) but bleeding-rates tended to be higher. Secondary: Not reported
Roe et al.[69] (2012) TRILOGY ACS Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who weighed <60 kg received 5 mg/day) vs clopidogrel 75 mg/day Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg	AC, DB, DD, event-driven, RCT Patients with ACS if selected for a final treatment strategy of medical management without revascularization within 10 days after the index event; patients with MI without ST-segment elevation had elevated cardiac markers and patients with unstable angina with negative cardiac markers had an ST-segment depression of >1 mm in ≥2 electrocardiographic leads, and patients had ≥1 of 4 risk criteria: age ≥60	N=7,243 (primary analysis; patients <75 years of age) N=2,083 (secondary analysis; patients ≥75 years of age) Up to 30 months	Primary: Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke among patients <75 years of age Secondary: Incidence of cardiovascular death, MI, and stroke; all-cause mortality; bleeding events; safety	Primary: At a median follow-up of 17 months, the primary endpoint occurred in 13.9 vs 16.0% of prasugrel- and clopidogrel-treated patients (HR in the prasugrel group, 0.91; 95% CI, 0.79 to 1.05; P=0.21). Similar results were observed in the overall population (18.7 vs 20.3%; HR, 0.96; 95% CI, 0.86 to 1.07; P=0.45). Because superiority was not established in the primary cohort, the prespecified testing strategy did not direct further superiority testing. The frequency of the primary end point in the two treatment groups did not differ significantly among prespecified subgroups of patients who were <75 years of age, but an interaction with prasugrel treatment was apparent in current or recent smokers, those who underwent angiography before randomization, and those taking a PPI at randomization. The prespecified analysis that was performed to account for multiple recurrent ischemic events suggested a lower risk among patients <75 years of age with prasugrel (HR, 0.85; 95% CI, 0.72 to 1.00; P=0.04). Among patients who had an ischemic event, 364 patients treated with prasugrel (10.1%) had at least one ischemic event compared to 397 patients (11.0%) with clopidogrel, whereas 77 (2.1%) vs 109 (3.0%) had a least two recurrent ischemic events, and 18 (0.5%) vs 24 (0.7%) had at least three recurrent ischemic events, respectively. Secondary: Among patients <75 years of age, there were no differences in the

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of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be treated with OL clopidogrel before randomization and were started on daily maintenance administration of a study drug after randomization.	years of age, the presence of diabetes, previous MI, or previous revascularization with either PCI or CABG			incidences of cardiovascular death (6.6 vs 6.8%; HR, 0.93; 95% CI, 0.75 to 1.15; P=0.48), MI (8.3 vs 10.5%; HR, 0.89; 95% CI, 0.74 to 1.07; P=0.21), and stroke (1.5 vs 2.2%; HR, 0.67; 95% CI, 0.42 to 1.06; P=0.08) between prasugrel- and clopidogrel-treated patients. Similar results were observed in the overall population (P=0.38, P=0.58, and P=0.52) Among patients <75 years of age, all-cause mortality was similar between the two treatments (7.8 vs 8.1%; HR, 0.96; 95% CI, 0.79 to 1.16; P=0.63). Similar results were observed in the overall population (P=0.40). At 30 months, the key bleeding end points of non-CABG-related severe or life-threatening events and major bleeding occurred with similar frequency among patients <75 years of age in the two treatment groups. The only subgroup in which there was a significant treatment interaction for TIMI major bleeding was patients receiving a reduced dose of aspirin. The frequency of new, benign neoplasms in the overall treated population did not differ significantly between prasugrel and clopidogrel (1.9 vs 1.8%; P=0.79); similar findings were observed among treated patients with no history of cancer or a history of previous cancer that had been cured before randomization. The incidence of common (>1.0%) nonhemorrhagic serious adverse events was balanced between the two treatments among patients <75 years of age, and the only significant difference observed was a higher rate of heart failure with clopidogrel.
Gurbel et al.[70] (2012) Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who weighed <60 kg received 5 mg/day) vs clopidogrel 75	Substudy of TRILOGY ACS Patients with ACS if selected for a final treatment strategy of medical management without revascularization within 10 days after the index event; patients with MI without ST-segment	N=2,564 Up to 30 months	Primary: Platelet reactivity (measured in $P2Y_{12}$ reaction units); composite of cardiovascular death, MI, or stroke through 30 months Secondary: Not reported	Primary: Among patients <75 years of age and weighing ≥60 kg, median $P2Y_{12}$ reaction unit values at 30 days were 64 (interquartile range, 33-128) with prasugrel compared to 200 (interquartile range, 141-260) with clopidogrel (P<0.001), a difference that persisted through all subsequent time points. Among patients <75 years of age and weighing <60 kg, corresponding values were 139 (interquartile range, 86 to 203) vs 209 (interquartile range, 148 to 283) (P<0.001). Among patients >75 years of age, corresponding values were 164 (interquartile range, 105 to 216) vs 222 (interquartile range, 148 to 268) (P<0.001). At 30 months, the rate of the composite endpoint was 17.2 (160 events) vs 18.9% (180 events) with prasugrel and clopidogrel (P=0.29). There were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be treated with OL clopidogrel before randomization and were started on daily maintenance administration of a study drug after randomization	elevation had elevated cardiac markers and patients with unstable angina with negative cardiac markers had an ST-segment depression of >1 mm in ≥2 electrocardiographic leads, and patients had ≥1 of 4 risk criteria: age ≥60 years of age, the presence of diabetes, previous MI, or previous revascularization with either PCI or CABG			no significant differences in the continuous distributions of 30 day $P2Y_{12}$ reaction unit values for patients with a primary efficacy endpoint compared to patients without an event (P=0.07) and no significant relationship between the occurrence of the primary efficacy endpoint and continuous $P2Y_{12}$ reaction unit values (adjusted HR for increase of 60 $P2Y_{12}$ reaction units, 1.03; 95% CI, 0.96 to 1.11; P=0.44). Similar findings were observed with 30 day $P2Y_{12}$ reaction unit cut points used to define high on-treatment platelet reactivity; $P2Y_{12}$ reaction unit >280 (adjusted HR, 1.16; 95% CI, 0.89 to 1.52; P=0.28) and $P2Y_{12}$ reaction unit >230 (adjusted HR, 1.20; 95% CI, 0.90 to 1.61; P=0.21). Secondary: Not reported
Wiviott et al.[71] (2013) TRILOGY ACS Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who weighed <60 kg received 5 mg/day) vs	Substudy of TRILOGY ACS Patients enrolled in the TRILOGY ACS trial stratified based on whether or not patients had coronary angiography before treatment	N=7,243 (primary analysis; patients <75 years of age) Up to 30 months	Primary: CV death, MI, or stroke at 30 months Secondary: All-cause mortality; bleeding events; safety; components of primary endpoint	Primary: Fewer patients who had angiography before enrolment reached the primary endpoint according to Kaplan-Meier analysis (12.8%) than did those who did not have angiography (16.5%; adjusted HR 0.63, 95% CI, 0.53 to 0.75; P<0.0001). Of the patients who had angiography before enrolment, fewer patients assigned to prasugrel reached the primary endpoint at 30 months compared with those assigned to clopidogrel (10.7% vs 14.9%; HR, 0.77; 95% CI, 0.61 to 0.98; P=0.032). We recorded no such difference at 30 months in patients who had not had pre-enrolment angiography (16.3% vs 16.7%; HR, 1.01; 95% CI, 0.84 to 1.20; P=0.94). For the difference in treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clopidogrel 75 mg/day Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be treated with OL clopidogrel before randomization and were started on daily maintenance administration of a study drug after randomization				effect between angiography cohorts, P=0.08. Secondary: A significantly smaller proportion of patients who had angiography before treatment also had cardiovascular death or all-cause death. GUSTO and TIMI bleeding did not differ significantly between groups. Prasugrel treatment in the angiography cohort, but not the no angiography cohort, was associated with fewer MIs and strokes than clopidogrel treatment. By contrast, the risk of CV death did not differ significantly between treatment groups in both angiography and no angiography cohorts.
Roe et al.[72] (2013) TRILOGY ACS Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who weighed <60 kg received 5 mg/day)	Substudy of TRILOGY ACS Patients enrolled in the TRILOGY ACS trial stratified based on age ≥75 or <75 years	N=7,243 (primary analysis; patients <75 years of age) N=2,083 (secondary analysis; patients ≥75	Primary: Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke Secondary: Incidence of	Primary: The Kaplan–Meier estimate of the primary efficacy end point through 30 months was >2.5-fold higher in participants ≥75 years of age compared with those <75 years of age (35.7 vs 14.9%; HR, 2.65; 95% CI, 2.37 to 2.97). The cumulative risk of the primary efficacy end point and non–CABG-related TIMI major bleeding through 30 months among participants ≥75 years of age was not significantly different with reduced-dose prasugrel compared with clopidogrel treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clopidogrel 75 mg/day Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be treated with OL clopidogrel before randomization and were started on daily maintenance administration of a study drug after randomization		years of age) Up to 30 months	cardiovascular death, MI, and stroke; all-cause mortality; bleeding events; safety	Secondary: The risk of non–CABG-related bleeding assessed with both GUSTO and TIMI bleeding scales was 2- to 3-fold higher with older age. Fatal bleeding events (1.1 vs 0.3%; HR, 4.31; 95% CI, 1.61 to 11.5) and intracranial hemorrhage (1.2 vs 0.6%; HR, 2.67; 95% CI, 1.33 to 5.37) were infrequent, but the risk was 3- to 4-fold higher in older and younger participants, respectively. The age-by-treatment interaction P value for stroke was 0.052 and for TIMI major/minor bleeding was 0.098. All other interaction P values were >0.1. Rates of intracranial hemorrhage (0.9 vs 1.5%; HR, 0.90; 95% CI, 0.30 to 2.67) and fatal bleeding (1.0 vs 1.1%; HR, 0.62; 95% CI, 0.15 to 2.59) were not significantly different between the prasugrel and clopidogrel groups.
Jackson et al.[73] (2016) TRILOGY ACS Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who	Substudy of TRILOGY ACS Patients included in this secondary analysis had a history of AF prior to or during the	N=710 (AF+) Compared to N=8,391 (AF-)	Primary: Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke	Primary: The unadjusted association of the primary composite endpoint of cardiovascular death, MI, or stroke occurred with increased risk in AF+ patients at 30 months: 31.1 vs 18.4% (HR, 1.61; 95% CI, 1.35 to 1.92; P<0.001). After adjustment, there was no difference in rates of the composite endpoint of cardiovascular death, MI, or stroke (HR, 1.16; 95% CI, 0.97 to 1.39; P=0.11).

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weighed <60 kg received 5 mg/day) vs clopidogrel 75 mg/day	index hospitalization and were not taking an oral anticoagulant	Up to 30 months	Secondary: Incidence of cardiovascular death, MI, and stroke; all-cause mortality; bleeding events; safety	Secondary: When all secondary outcomes were evaluated, there was a significantly increased risk of events, particularly stroke, in AF+ patients at 30 months, although the overall incidence of stroke was low. The rate of all-cause death was significantly higher in AF+ patients at 30 months: 18.1 vs 11.1% (HR, 1.62; 95% CI, 1.30 to 2.02; P<0.001). Rates of all-cause death were also similar between AF+ and AF− patients (HR, 1.10; 95% CI, 0.87 to 1.39; P=0.42). Rates of major bleeding at 30 months were similar between both AF groups.
Bonaca et al.[74] (2015) PEGASUS-TIMI 54 Ticagrelor 90 mg twice daily vs ticagrelor 60 mg twice daily vs placebo	DB, MC, RCT Patients had had a spontaneous MI one to three years before enrollment, were ≥50 years of age, and had one of the following additional high-risk features: age ≥65 years, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance <60 ml/minute	N=21,162 Median of 33 months	Primary: Composite of cardiovascular death, myocardial infarction, or stroke; Thrombolysis in Myocardial Infarction (TIMI) major bleeding Secondary: cardiovascular death and death from any cause	Primary: The two ticagrelor doses each significantly reduced, as compared with placebo, the rate of the primary composite end point. Kaplan–Meier rates at three years were 7.85% in the group that received 90 mg of ticagrelor twice daily, 7.77% in the group that received 60 mg of ticagrelor twice daily, and 9.04% in the placebo group (HR for 90 mg of ticagrelor vs placebo, 0.85; 95% CI, 0.75 to 0.96; P=0.008; HR for 60 mg of ticagrelor vs placebo, 0.84; 95% CI, 0.74 to 0.95; P=0.004). The rate of the primary safety end point of TIMI major bleeding was higher with the two ticagrelor doses than with placebo. Kaplan–Meier rates at three years were 2.60% in the group that received 90 mg of ticagrelor, 2.30% in the group that received 60 mg of ticagrelor, and 1.06% in the placebo group (HR for 90 mg of ticagrelor vs placebo, 2.69; 95% CI, 1.96 to 3.70; P<0.001; HR for 60 mg of ticagrelor vs placebo, 2.32; 95% CI, 1.68 to 3.21; P<0.001) Secondary: There was a trend with ticagrelor toward a reduction in the rate of cardiovascular death alone, but this effect was not significant. Therefore, on the basis of the prespecified hierarchical testing procedure, the assessment of all the other efficacy end points was considered to be exploratory. The rate of death from any cause did not differ significantly with either ticagrelor dose, as compared with placebo.
Wallentin et al.[75] (2009)	AC, DB, DD, MC, PG, PRO, RCT	N=18,624	Primary: Composite	Primary: At 12 months, ticagrelor was associated with significantly fewer

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.	Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation	12 months	endpoint of the rate of vascular death, MI, or stroke; major bleeding Secondary: Effect in patients for whom invasive treatment was planned; composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; individual components of the primary endpoint; all-cause mortality; other bleeding events; dyspnea; bradyarrhythmia; any other adverse event; results of laboratory safety tests	composite events compared to clopidogrel (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.92; P<0.001). A treatment effect was seen within 30 days and persisted throughout the trial. The rate of major bleeding was not different between ticagrelor and clopidogrel (11.6 vs 11.2%; HR, 1.04; 95% CI, 0.95 to 1.13; P=0.43). Secondary: In patients undergoing invasive procedures, significantly fewer composite events occurred with ticagrelor (8.9 vs 10.6%; HR, 8.4; 95% CI, 0.75 to 0.94; P=0.003). Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (10.2 vs 12.3%; HR, 0.84; 95% CI, 0.77 to 0.92; P<0.001). Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other thrombotic event (14.6 vs 16.7; HR, 0.88; 95% CI, 0.81 to 0.95; P<0.001). The rates of MI (5.8 vs 6.9%; HR, 0.84; 95% CI, 0.75 to 0.95; P=0.005) and vascular death (4.0 vs 5.1%; HR, 0.84; 95% CI, 0.69 to 0.91; P=0.001) were significantly lower with ticagrelor. The rate of stroke was not different between the two treatments (1.5 vs 1.3%; HR, 1.17; 95% CI, 0.91 to 1.52; P=0.22). The rate of all-cause mortality was significantly lower with ticagrelor (4.5 vs 5.9%; HR, 0.78; 95% CI, 0.69 to 0.89; P<0.001). Data on minor bleeding events were not reported. Rates of fatal bleeding were not different between the two treatments (0.3 vs 0.3%; HR, 0.87; 95% CI, 0.48 to 1.59; P=0.66). The rate of fatal non-intracranial bleeding was significantly higher with clopidogrel (0.3 vs 0.1%, respectively; P=0.03). The rate of fatal intracranial bleeds was significantly higher with ticagrelor (0.10 vs 0.01%, respectively; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The rate of dyspnea was significantly higher with ticagrelor (13.8 vs 7.8%; HR, 1.84; 95% CI, 1.68 to 2.02; P<0.001). From this group, 0.9 and 0.1% of patients discontinued treatment (HR, 6.12; 95% CI, 3.41 to 11.01; P<0.001). Rates of pacemaker insertion (P=0.87), syncope (P=0.08), bradycardia (P=0.21) and heart block (P=1.00) were not different between the two treatments. Laboratory testing revealed significant increases in baseline serum uric acid with ticagrelor at one (P<0.001) and 12 months (P<0.001). Similar results were observed with serum creatinine (P<0.001 for both). One month after the end of treatment, there were no differences between the two treatments for either serum uric acid (P=0.56) or creatinine (P=0.59).
James et al. [76] (2011) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation, undergoing noninvasive procedures	N=5,216 12 months	Primary: Composite endpoint of the rate of vascular death, MI, or stroke; major bleeding events Secondary: Individual components of the primary composite endpoint; all-cause mortality; nonvascular mortality; composite of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other	Primary: At 12 months, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (12.0 vs 14.3%; HR, 0.85; 95% CI, 0.73 to 1.00; P=0.045). The rate of major bleeding did not differ between ticagrelor and clopidogrel (11.9 vs 10.3%; HR, 1.17; 95% CI, 0.98 to 1.39; P=0.079). Secondary: The rate of vascular death was significantly lower with ticagrelor (5.5 vs 7.2%; HR, 0.76; 95% CI, 0.61 to 0.96; P=0.019). The rates of MI (7.2 vs 7.8%; HR, 0.94; 95% CI, 0.77 to 1.15; P=0.555) and stroke (2.1 vs 1.7%; HR, 1.35; 95% CI, 0.89 to 2.07; P=0.162) were not different between the two treatments. The rates of all-cause mortality was significantly lower with ticagrelor (6.1 to 8.2%; HR, 0.75; 95% CI, 0.61 to 0.93; P=0.010). The rate of nonvascular death was not different between the two treatments (0.6 vs 1.0%; HR, 0.68; 95% CI, 0.35 to 1.31; P=0.252). The rate of the composite of vascular death, MI, stroke, composite ischemic events, or other arterial thrombotic events was not different

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.			arterial thrombotic event; subclasses of stroke; other bleeding events	between the two treatments (18.6 vs 20.3%; HR, 0.94; 95% CI, 0.82 to 1.06; P=0.309). The rates of ischemic (1.5 vs 1.4%; P=0.530), hemorrhagic (0.5 vs 0.2%; P=0.069) or unknown (0.20 vs 0.06%; P=0.124) strokes were not different between the two treatments. The rates of life threatening or fatal (5.5 vs 5.6%; HR, 0.99; 95% CI, 0.77 to 1.26; P=0.911) and intracranial bleeding (0.5 vs 0.2%; HR, 2.83; 95% CI, 0.90 to 8.90; P=0.075) were not different between the two treatments. The rate of other major bleeding was significantly higher with ticagrelor (6.8 vs 4.9%; HR, 1.38; 95% CI, 1.09 to 1.76; P=0.009). The rates of non-CABG-related (P=1.03), CABG-related (P=0.335), coronary procedure related (P=0.231), noncoronary procedure related (P=0.072) bleeding were not different between the two treatments. The rate of major and minor bleeding was significantly higher with ticagrelor (16.4 vs 14.4%; HR, 1.17; 95% CI, 1.01 to 1.36; P=0.0358).
Cannon et al.[77] (2010) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation, undergoing invasive procedures	N=13,408 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; total major bleeding Secondary: Composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other	Primary: At 12 months, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (9.0 vs 10.7%; HR, 0.84; 95% CI, 0.75 to 0.94; P=0.0025). The rate of major bleeding did not differ between ticagrelor and clopidogrel (P=0.8803). Secondary: Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (9.4 vs 11.2%; HR, 0.84; 95% CI, 0.75 to 0.94; P=0.0016). Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, composite ischemic events or other arterial thrombotic events (9.4 vs 11.2%; HR, 0.85; 95% CI, 0.77 to 0.93; P=0.0005). The rates of MI (5.3 vs 6.6%; HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0023) and vascular death (3.4 vs 4.3%; HR, 0.82; 95% CI, 0.68 to 0.98;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.			arterial thrombotic event; components of the primary endpoint; all-cause mortality; stent thrombosis; other bleeding events; safety	P=0.0250) were significantly lower with ticagrelor. The rate of stroke was not different between the two treatments (1.2 vs 1.1%; HR, 1.08; 95% CI, 0.78 to 1.50; P=0.6460). The rate of all-cause mortality was significantly lower with ticagrelor (3.9 vs 5.0%; HR, 0.81; 95% CI, 0.68 to 0.95; P=0.0054). The rates of definite (1.3 vs 2.0%; HR, 0.64; 95% CI, 0.46 to 0.88; P=0.0054), definite or probable (2.2 vs 3.0%; HR, 0.73; 95% CI, 0.57 to 0.94; P=0.0142) and total (definite, probable or possible) (2.8 vs 3.8%; HR, 0.73; 95% CI, 0.59 to 0.92; P=0.0068) stent thrombosis were significantly lower with ticagrelor. The rates of life-threatening or fatal (P=0.6095), intracranial (P=0.4364) and other major bleeding (P=0.4030) were not different between the two treatments. The rates of total major or minor (P=0.0700), CABG-related (P=0.0710), coronary procedure-related (P=0.7768) and noncoronary procedure-related (P=0.3998) bleeding were not different between the two treatments. The rate of non-CABG-related bleeding was significantly higher with ticagrelor (8.9 vs 7.1%; HR, 1.26; 95% CI, 1.11 to 1.43; P=0.0004). The rate of dyspnea was significantly higher with ticagrelor (13.9 vs 8.0%; P<0.0001). Of the patients experiencing dyspnea, 0.8 and 0.2% discontinued treatment (P value not reported).
Steg et al.[78] (2010) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg	Substudy of the PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with ST-segment elevation or left bundle-branch block	N=7,544 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding Secondary: Composite endpoint of vascular death or MI (excluding	Primary: At 12 months, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (9.4 vs 10.8%; HR, 0.87; 95% CI, 0.75 to 1.01; P=0.07). The rate of major bleeding did not differ between ticagrelor and clopidogrel (HR, 0.98; 95% CI, 0.8 to 1.14; P=0.76). Secondary: Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death and MI (8.4 vs 10.2%; HR, 0.82; 95% CI, 0.71 to 0.69; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.			silent); composite endpoint of all-cause mortality, MI (excluding silent), or stroke; composite endpoint of vascular death, total MI, stroke, severe recurrent cardiac ischemia, recurrent ischemia, TIA, or other arterial thrombotic events; components of the primary endpoint; all-cause mortality; severe recurrent cardiac ischemia; recurrent ischemia; TIA; arterial thrombotic events; stent thrombosis; safety	Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (9.8 vs 11.3%; HR, 0.87; 95% CI, 0.75 to 1.00; P=0.05). Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, composite ischemic events or other arterial thrombotic events (13.3 vs 15.0%; HR, 0.87; 95% CI, 0.77 to 0.99; P=0.03). The rates of MI (4.7 vs 5.8%; HR, 0.80; 95% CI, 0.65 to 0.98; P=0.03) and stroke (1.7 vs 1.0%; HR, 1.63; 95% CI, 1.07 to 2.48; P=0.02) were significantly lower with ticagrelor, but not vascular death (4.5 vs 5.5%; HR, 0.83; 95% CI, 0.67 to 1.02; P=0.07). The rate of all-cause mortality was significantly lower with ticagrelor (5.0 vs 6.1%; HR, 0.82; 95% CI, 0.67 to 1.00; P=0.05). The rates of severe recurrent cardiac ischemia (2.7 vs 3.2%; HR, 0.81; 95% CI, 0.61 to 1.06; P=0.13), TIA (0.2 vs 0.2%; P value not reported) and arterial thrombotic events (0.3 vs 0.4%; HR, 0.65; 95% CI, 0.28 to 1.51; P=0.32) were not different between the two treatments. The rate of recurrent ischemia was significantly lower with ticagrelor (4.3 vs 5.1%; HR, 0.81; 95% CI, 0.65 to 1.01; P=0.05). The rates of definite or probable stent thrombosis was not different between the two treatments (2.6 vs 3.4%; HR, 0.74; 95% CI, 0.55 to 1.00; P=0.05). The rates of definite, probable or possible (3.3 vs 4.3%; HR, 0.75; 95% CI, 0.57 to 0.99; P=0.04) and definite (1.6 vs 2.4%; HR, 0.66; 95% CI, 0.45 to 0.95; P=0.03) stent thromboses were significantly lower with ticagrelor. The rates of fatal (P value not reported), life-threatening (P=0.86), major (P=0.76), major and minor (P=0.43), CABG-related (major; P=0.30, major and minor; P=0.26), non-CABG-related (major; P=0.61, major and minor; P=0.11), procedure-related (major; P=0.83, major and minor; P=0.72) and major non-procedure-related (P=0.30) bleeding were not different between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the two treatments. The rate of non-procedure-related major and minor bleeding was significantly lower with clopidogrel (5.1 vs 3.7%; HR, 1.31; 95% CI, 1.04 to 1.66; P=0.02). The rate of dyspnea was significantly higher with ticagrelor (12.6 vs 8.4%; P<0.0001), and caused significantly more treatment discontinuations (0.5 vs 0.1%; P=0.0004). Rates of bradycardia (P=0.83), syncope (P=0.18), heart block (P=0.64) and pacemaker insertion (P=0.20) were not different between the two treatments.
James et al.[79] (2010) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose.	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation and chronic kidney disease (creatine clearance <60 mL/minute)	N=15,202 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding Secondary: All-cause mortality, other bleeding events, safety	Primary: In patients with chronic kidney disease, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (17.3 vs 22.0%; HR, 0.77; 95% CI, 0.65 to 0.90; P=0.13). In patients with chronic kidney disease, there was no difference in the rate of major bleeding between ticagrelor and clopidogrel (15.1 vs 14.3%; HR, 1.07; 95% CI, 0.88 to 1.03; P=0.92). Secondary: In patients with chronic kidney disease, the rate of all-cause mortality was not different between the two treatments (10.0 vs 14.0%; HR, 0.72; 95% CI, 0.58 to 0.89; P=0.16). In patients with chronic kidney disease, the rates of major or minor (P=0.54), non-CABG-related major (P=0.77), fatal major (P=0.06) and intracranial bleeding (P=0.69) were not different between the two treatments. In patients with chronic kidney disease, the rate of dyspnea was significantly less with clopidogrel (16.4 vs 11.5%; HR, 1.54; 95% CI, 1.27 to 1.88; P=0.04). In patients with chronic kidney disease, the rate of ventricular pauses was no different between the two treatments (5.4 vs 4.6%; HR, 1.16; 95% CI, 0.51 to 2.52; P=0.56).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
In patients receiving a stent, 325 mg was allowed for six months.				
James et al.[80] (2010) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation and diabetes	N=4,662 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding Secondary: All-cause mortality, MI, definite stent thrombosis, other bleeding events	Primary: In patients with diabetes, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (14.1 vs 16.2%; HR, 0.88; 95% CI, 0.76 to 1.03). In patients with diabetes, there was no difference in the rate of major bleeding between ticagrelor and clopidogrel (14.1 vs 14.8%; HR, 0.95; 95% CI, 0.81 to 1.12). Secondary: In patients with diabetes, the rate of all-cause mortality was not different between the two treatments (7.0 vs 8.7%; HR, 0.82; 95% CI, 0.66 to 1.01). In patients with diabetes, the rate of MI was not different between the two treatments (8.4 vs 9.1%; HR, 0.92; 95% CI, 0.75 to 1.13). In patients with diabetes, the rate of definite stent thrombosis was not different between the two treatments (1.6 vs 2.4%; HR, 0.65; 95% CI, 0.36 to 1.17). In patients with diabetes, the rates of non-CABG-related major (5.5 vs 4.9%; HR, 1.13; 95% CI, 0.86 to 1.49) and CABG-related major bleeding (9.3 vs 10.4%; HR, 0.90; 95% CI, 0.74 to 1.09) were not different between the two treatments.
Held et al.[81]	RETRO substudy of	N=1,261	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.	PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation who underwent CABG	12 months	Composite endpoint of vascular death, MI, or stroke after CABG; major CABG-related bleeding Secondary: Individual components of the primary endpoint after CABG; all-cause mortality after CABG; other bleeding events after CABG	There was no difference between ticagrelor and clopidogrel with regards to the primary composite endpoint (10.6 vs 13.1%; HR, 0.84; 95% CI, 0.60 to 1.16; P=0.2862). There was no difference between ticagrelor and clopidogrel in the rate of major CABG-related bleeding (81.3 vs 80.1%; HR, 1.01; 95% CI, 0.90 to 1.15; P=0.84). Secondary: Rates of MI (excluding silent) (6.0 vs 5.7%; HR, 1.06; 95% CI, 0.66 to 1.68; P=0.8193) and stroke (2.1 vs 2.1%; HR, 1.17; 95% CI, 0.53 to 2.62; P=0.6967) were not different between the two treatments. The rate of vascular death was significantly less with ticagrelor (4.1 vs 7.9%; HR, 0.52; 95% CI, 0.32 to 0.85; P=0.0092). The rate of all-cause mortality was significantly less with ticagrelor (4.7 vs 9.7%; HR, 0.49; 95% CI, 0.32 to 0.77; P=0.0018). The rates of life-threatening or fatal CABG-related bleeding were not different between the two treatments (42.6 vs 43.7%; HR, 1.02; 95% CI, 0.87 to 1.21; P=0.77).
Wallentin et al.[82] (2010) PLATO Ticagrelor 180 mg loading dose,	Genetic (CYP 2C19 and ABCB1) substudy of PLATO Adult patients hospitalized with	N=10,285 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding (loss-of-	Primary: In patients with any loss-of-function allele, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (8.3 vs 10.7%; HR, 0.77; 95% CI, 0.60 to 0.99; P=0.0380). In patients with any loss-of-function allele, there was no difference in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.	documented ACS within the previous 24 hours, with or without ST-segment elevation		function allele) Secondary: Composite endpoint of vascular death or MI, definite stent thrombosis, major bleeding (gain-of-function allele), other bleeding events, net clinical benefit	rate of major bleeding between ticagrelor and clopidogrel (10.8 vs 10.4%; HR, 1.04; 95% CI, 0.82 to 1.30; P=0.77). Secondary: In patients with any loss-of-function allele, ticagrelor was association with significantly fewer events with regards to the composite of vascular death or MI (7.4 vs 9.9%; HR, 0.73; 95% CI, 0.51 to 0.95; P=0.0184). In patients with any loss-of-function allele, the rate of definite stent thrombosis was not different between the two treatments (1.6 vs 2.2%; HR, 0.71; 95% CI, 0.36 to 1.37; P=0.30). In patients with any gain-of-function allele, the rate of major bleeding was not different between the two treatments (9.5 vs 10.8%; HR, 0.86; 95% CI, 0.71 to 1.05; P=0.13). In patients with any loss-of-function allele, the rates of non-CABG-related major (4.1 vs 3.0%; HR, 1.39; 95% CI, 0.93 to 2.08; P=0.11) and CABG-relate major bleeding (7.0 vs 7.8%; HR, 0.87; 95% CI, 0.66 to 1.14; P=0.31) were not different between the two treatments. In patients with any loss-of-function allele, the net clinical benefit was not different between the two treatments (14.7 vs 16.6%; HR, 0.88; 95% CI, 0.72 to 1.06; P=0.17). In patients with no loss-of-function, clopidogrel was significantly favored (13.4 vs 15.2%; HR, 0.86, 95% CI, 0.76 to 0.97; P=0.0172).
Mahaffey et al.[83] (2011) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation who received treatment in the United States	N=1,413 12 months	Primary: Composite endpoint of the vascular death, MI, or stroke; major bleeding Secondary: Individual components of the primary composite	Primary: Within the United States, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 1.75; P=0.1459). For the rest of world, ticagrelor was significantly favored (9.0 vs 11.0%; HR, 0.81; 95% CI, 0.74 to 0.90; P<0.001). Within the United States, there was no difference in the rates of major bleeding between ticagrelor and clopidogrel (11.3 vs 11.0%; HR, 1.05; 95% CI, 0.76 to 1.45; P=0.7572).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.			endpoint, all-cause mortality, other bleeding events	Secondary: Within the United States, the rates of vascular death (3.4 vs 2.7%; HR, 1.26; 95% CI, 0.69 to 2.31; P=0.4468), MI (9.1 vs 6.7%; HR, 1.38; 95% CI, 0.95 to 2.01; P=0.0956) and stroke (1.0 vs 0.6%; HR, 1.75; 95% CI, 0.51 to 0.597; P=0.3730) were not different between the two treatments. For the rest of world, ticagrelor was significantly favored for reducing vascular death (3.8 vs 4.9%; HR, 0.77; 95% CI, 0.67 to 0.89; P=0.0005) and MI (5.1 vs 6.4%; HR, 0.80; 95% CI, 0.70 to 0.90; P=0.0004). Within the United States, the rate of all-cause mortality was not different between the two treatments (4.0 vs 3.4%; HR, 1.17; 95% CI, 0.68 to 2.01; P=0.5812). For the rest of world, ticagrelor was significantly favored (4.3 vs 5.6%; HR, 0.77; 95% CI, 0.67 to 0.88; P=0.0001). Within the United States, the rates of non-CAGB-related major (4.3 vs 3.7%; HR, 1.20; 95% CI, 0.70 to 2.04; P=0.5115) and major or minor bleeding (14.8 vs 13.6%; HR, 1.11; 95% CI, 0.84 to 1.84; P=0.4599) were not different between the two treatments. For the rest of the world, clopidogrel was significantly favored (3.9 vs 3.3%; HR, 1.19; 95% CI, 1.01 to 1.39; P=0.0330 and 14.5 vs 13.2%; HR, 1.11; 95% CI, 1.02 to 1.20; P=0.0114). For the entire population, results for the overall cohort yields an HR of 1.45 (95% CI, 1.01 to 2.09) favoring clopidogrel for maintenance aspirin doses ≥300 mg/day and HR of 0.77 (95% CI, 0.69 to 0.86) favoring ticagrelor for a maintenance aspirin dose ≤100 mg/day. The interaction between aspirin dose category and treatment is significant (P=0.00006). Within the United States, for patients receiving daily aspirin doses ≥300 mg, the event rate was 40 vs 27 with ticagrelor and clopidogrel (HR, 1.62; 95% CI, 0.99 to 2.94). The event rate was 19 vs 24 in patients receiving ≤100 mg/day of aspirin (HR, 0.73; 95% CI, 0.40 to 1.33).
Storey et al.[84] (2011) PLATO Ticagrelor 180 mg loading dose,	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous	N=199 12 months	Primary: FEV_1 after the completion of study treatment (six, nine, or 12 months depending	Primary: FEV_1 values at the different evaluated time points were similar between treatments before and 20 minutes after inhalation of a β agonist (P values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.	24 hours, with or without ST-segment elevation		on phase of entry into the PLATO trial) Secondary: FEV_1 after one month of treatment and one month after the discontinuation of treatment, other measures of pulmonary function, safety	There was no apparent change in FEV_1 before and 20 minutes after inhalation of a β agonist over time with either treatment and after the discontinuation of the study medication (P value not reported). Similar numbers of ticagrelor- and clopidogrel-treated patients showed >10% improvement in FEV_1 over time (seven and 12), with similar numbers of these patients showing improvement at the first visit after inhaled β agonist. The results of other pulmonary function parameters were also similar between the two treatments, with no apparent change over time and after discontinuation of study medication. Dyspnea or heart failure was noted in six and seven patients receiving ticagrelor and clopidogrel; pulmonary function parameters for these patients were consistent with findings in the rest of the treatment cohorts.
James et al.[85] (2012) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs	Substudy of PLATO Adult patients with and without a history of prior stroke or TIA and who were hospitalized with documented ACS within the previous 24 hours, with or	N=18,624 12 months	Primary: Composite endpoint of the vascular death, MI or stroke and major bleeding Secondary: Components of primary composite endpoint and all-	Primary: A total of 1,152 patients (6.2%) had a history of stroke or TIA. Overall, patients with prior history of stroke had higher rates of the primary composite endpoint compared to those without prior stroke or TIA; however, safety and efficacy in these patients were similar in the overall study population. The RR reduction of the primary composite endpoint with ticagrelor compared to clopidogrel was similar in patients with (HR, 0.87) and without (HR, 0.84) prior stroke or TIA (P=0.84).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.	without ST-segment elevation		cause mortality	The risk of major bleeding with ticagrelor vs clopidogrel in patients with prior history of stroke or TIA was similar in patients without prior history (P=0.77). Secondary: When comparing patients with prior history of stroke or TIA to those without prior history, the RR reduction of cardiovascular death (P=0.42), MI (P=0.19) and overall stroke (P=0.89) was similar. The HR of all-cause mortality with ticagrelor compared to clopidogrel was 0.62 in patients with prior stroke or TIA and 0.81 in those without a prior history (P=0.19).
Kotsia et al.[86] (2014) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD	Substudy of PLATO Patients enrolled in the PLATO trial with extensive CAD (defined as 3-vessel disease, left main disease, or prior CABG irrespective of graft patency)	N=15,388 (4,646 with extensive CAD; 10,742 without extensive CAD) 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; total major bleeding Secondary: Composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe	Primary: Patients with extensive CAD had 2.32-fold higher risk for the primary composite end point compared with those without extensive CAD (16.3 vs 7.4%, P<0.0001). Ticagrelor, compared with clopidogrel, reduced the composite end point to a similar extent by 15% both in patients with extensive CAD (14.9 vs 17.6%; HR, 0.85; 95% CI, 0.73 to 0.98) and in patients without extensive CAD (6.8 vs 8.0%; HR, 0.85; 95% CI, 0.74 to 0.98; P=0.99). The absolute risk reduction with the use of ticagrelor was higher in patients with extensive CAD compared with patients without extensive CAD (2.7 vs 1.2%, respectively). Major bleeding was similar with ticagrelor vs clopidogrel among patients without (7.3 vs 6.4%; HR, 1.14; 95% CI, 0.98 to 1.33) and with (25.7 vs 25.5%; HR, 1.02; 95% CI, 0.90 to 1.15; P =0.24) extensive CAD.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.			recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; components of the primary endpoint; all-cause mortality; stent thrombosis; other bleeding events; safety	Secondary: The absolute risk reduction in all-cause death was higher in patients with extensive CAD compared with patients without extensive CAD (2.3 vs 0.6%, respectively). There was also a similar relative decrease with the use of ticagrelor, regardless of CAD extent, in all-cause mortality (24% in patients with extensive CAD vs 16% in patients without extensive CAD; P=0.53), MI (12 vs 20%; P=0.44), and stent thrombosis (20 vs 29%, P=0.57).
Brilakis et al.[87] (2013) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.	Substudy of PLATO Patients enrolled in the PLATO trial who had undergone prior CABG	N=1,133 (prior CABG) N=17,480 (no prior CABG) 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; total major bleeding Secondary: Composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic	Primary: The incidence of the primary end point was reduced by ticagrelor by 16% in patients without prior CABG (9.2% ticagrelor vs 11.0% clopidogrel) and by 10% in patients with prior CABG (19.6 vs 21.4%; P =0.66). The incidence of MI was reduced by 16% in patients without prior CABG and by 9% in patients with prior CABG. The incidence of major bleeding was similar in patients receiving ticagrelor vs clopidogrel in both the prior-CABG and the no-prior-CABG subgroup. The adjusted hazard ratio for the primary end point for ticagrelor vs clopidogrel in the prior-CABG and no-prior-CABG groups was 0.91 (95% CI, 0.67 to 1.24) for prior CABG and 0.86 (95% CI, 0.77 to 0.96) for no prior CABG (P=0.7347). Secondary: The adjusted HR for all-cause death was 1.17 (95% CI, 0.72 to 1.89) for prior CABG and 0.82 (95% CI, 0.70 to 0.96) for no prior CABG (P=0.1757); and that for major bleed was 0.89 (95% CI, 0.55 to 1.47) for prior CABG and 1.08 (95% CI, 0.98 to 1.20) for no prior CABG (P=0.4570).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six months.			event; components of the primary endpoint; all-cause mortality; stent thrombosis; other bleeding events; safety	
Kohli et al.[88] (2013) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading	Substudy of PLATO Patients enrolled in the PLATO trial who experienced a primary end point event during follow-up for 6 to 12 months	N=1,570 (developed one event) N=318 (recurrent events) 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; total major bleeding Secondary: Composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; components of the primary endpoint; all-cause mortality; stent thrombosis; other	Primary: The first occurrence of the primary end point of the trial (CVD/MI/stroke) was reduced (HR, 0.84; 95% CI, 0.77 to 0.92; P<0.001) in patients on ticagrelor as compared with clopidogrel. The hazard for the time to second occurrence of this composite end point or all-cause death was also significantly reduced by ticagrelor (HR, 0.80; 95% CI, 0.70 to 0.90; P<0.001). With respect to total number of events during the trial, ticagrelor resulted in fewer total CVD/MI/Stroke events as compared to clopidogrel (1057 vs 1225; NNT=54). Beyond the first event, there were numerically fewer additional events with ticagrelor (189 vs 205; P=0.40). Potent platelet inhibition resulted in no difference in first, second, or total occurrences of major bleeding. In an on-treatment cohort, there were 961 first occurrences of PLATO major bleeding events with ticagrelor, compared with 929 with clopidogrel (HR, 1.04; P=0.43). Secondary: Ticagrelor also effectively reduced the hazard for time to first of any atherothrombotic event to 0.88 (95% CI, 0.82 to 0.95; P<0.001). Recurrent events were similarly reduced (740 vs 834; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose. In patients receiving a stent, 325 mg was allowed for six months.			bleeding events; safety	
Patel et al.[89] (2015) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for six	Substudy of PLATO Patients enrolled in the PLATO trial stratified according to reported PAD status at baseline	N=18,624 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; total major bleeding Secondary: Not reported	Primary: At one year, CV death, MI, or stroke occurred in 19.3% of patients with PAD (n=1144) compared to 10.2% in patients without PAD (P<0.001). The Kaplan-Meier one year event rate for the primary composite endpoint in PAD patients treated with ticagrelor as compared with clopidogrel, was 18 vs 20.6% (HR, 0.85; 95% CI, 0.64 to 1.11; for PAD status by treatment interaction, P=0.99) and for death from any cause 8.7 vs 11.9%, (HR, 0.74; 95% CI, 0.50 to 1.08; interaction P=0.73). PLATO-defined major bleeding event rates at one year were 14.8% for ticagrelor compared to 17.9% for clopidogrel, (HR, 0.81; 95% CI, 0.59 to 1.10; interaction P=0.09). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months.				
Jackson et al.[90] (2015) TRANSLATE-ACS Aspirin plus anticoagulant plus clopidogrel (triple-C) vs aspirin plus anticoagulant plus prasugrel (triple-P) vs aspirin plus clopidogrel (dual-C) vs aspirin plus prasugrel (dual-P)	OBS, PRO Patients in the United States who had either ST-segment elevation myocardial infarction (STEMI) or non-STEMI treated with PCI and a $P2Y_{12}$ receptor inhibitor during their index hospitalization	N=11,756 15 months	Primary: Post-discharge bleeding and major adverse cardiovascular events (MACE) during the 6-month follow-up period after the index MI hospitalization Secondary: Not reported	Primary: Of 11,756 MI patients, 526 (4.5%) were discharged on triple-C, 91 (0.8%) on triple-P, 7,715 (66%) on dual-C, and 3,424 (29%) on dual-P. At six months post-discharge, triple-C was associated with a significantly higher risk of any BARC-defined bleeding compared with dual-C after multivariable analysis (28.7 vs 19.7%; adjusted incidence rate ratio [IRR], 1.68; 95% CI, 1.29 to 2.18; P=0.0001). Similarly, triple-P was associated with significantly higher any BARC bleeding compared with dual-P (38.5 vs 26.7%; adjusted IRR, 1.88; 95% CI, 1.10 to 3.20; P=0.02). Among patients treated with triple therapy, triple-P was associated with significantly higher bleeding compared with triple-C (39.0 vs. 24.4%; adjusted IRR, 2.37; 95% CI, 1.36 to 4.15; P=0.003). There were no statistically significant differences in risk-adjusted MACE between groups. Secondary: Not reported
Tricoci et al.[12] (2012) TRACER Vorapaxar loading dose of 40 mg and a daily maintenance dose of 2.5 mg thereafter vs placebo	DB, MC, RCT Adults with acute symptoms of coronary ischemia within 24 hours before hospital presentation and at least one of the following findings: a cardiac troponin or creatine kinase MB level that was higher	N=12,944 Median follow-up period of 502 days	Primary: Composite of death from CV causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization; composite of moderate or severe bleeding according to the GUSTO	Primary: The primary efficacy endpoint corresponded to a 2-year rate of 18.5% in the vorapaxar group and 19.9% in the placebo group (HR in the vorapaxar group, 0.92; 95% CI, 0.85 to 1.01; P=0.07). Vorapaxar increased the rate of GUSTO moderate or severe bleeding, as compared with placebo (7.2 vs 5.2%; HR, 1.35; 95% CI, 1.16 to 1.58; P<0.001). The rate of clinically significant TIMI bleeding was increased among patients treated with vorapaxar (20.2 vs 14.6%; HR, 1.43; 95% CI, 1.31 to 1.57; P<0.001). The excess bleeding events continued to accrue during follow-up. The vorapaxar group also had higher rates of GUSTO severe bleeding (P<0.001), TIMI major bleeding (P<0.001), and intracranial hemorrhage (P<0.001), with an incremental risk over time.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Either treatment in addition to physician-guided standard therapy	than the upper limit of the normal range or new ST-segment depression or transient ST-segment elevation (<30 minutes). Also required were one or more of the following four criteria: age ≥ 55 years; previous MI, PCI, or CABG; diabetes mellitus; or PAD.		classification and clinically significant bleeding according to the TIMI classification Secondary: Composite of death from CV causes, MI, or stroke	Rates of CABG-related bleeding during the index hospitalization did not differ significantly between the two study groups, and rates of reoperation for bleeding and fatal bleeding were similar. Secondary: The key secondary end point occurred in 822 patients in the vorapaxar group and 910 patients in the placebo group, for 2-year Kaplan–Meier estimates of 14.7% and 16.4%, respectively (HR, 0.89; 95% CI, 0.81 to 0.98; P=0.02). Among the individual components of the efficacy end points, the reduction in the rate of MI was the main effect observed in the vorapaxar group, as compared with the placebo group (11.1 vs 12.5% at 2 years; HR, 0.88; 95% CI, 0.79 to 0.98; P=0.02). A reduction in the rate of type 1 (spontaneous) MI in the vorapaxar group largely accounted for the difference (5.6 vs 6.8%).
Leonardi et al.[91] (2013) TRACER Vorapaxar loading dose of 40 mg and a daily maintenance dose of 2.5 mg thereafter vs placebo Either treatment in addition to physician-guided standard therapy	Outcome analysis of TRACER (exploratory subanalysis) Patients enrolled in the TRACER trial with an outcome of MI	N=12,944 (1,580 MIs occurred, including recurrent events) Median follow-up period of 502 days	Primary: First occurrence of MI, incidence of MI Secondary: Not reported	Primary: Compared with placebo, vorapaxar reduced the hazard of a first MI of any type by 12% (HR, 0.88; 95% CI, 0.79 to 0.98; P=0.021). The effect of vorapaxar was similar when the endpoint included all MIs, including recurrent MIs after the first event (HR 0.86; 95% CI, 0.77 to 0.97; P=0.014). A type 1 (spontaneous) MI occurred in 5.9% of patients in the vorapaxar group and in 7.0% of patients of the placebo group (HR, 0.83; 95% CI, 0.73 to 0.95; P=0.007). Vorapaxar effect on MI was consistent across key subgroups, and no interaction test was statistically significant. Secondary: Not reported
Whellan et al.[92] (2014) TRACER	Subgroup analysis of TRACER Patients enrolled in	N=1,312 (of 12,944 total patients; 10.1%)	Primary: Composite of death from CV causes, MI, stroke,	Primary: In patients undergoing CABG during index hospitalization (N=1,312), the primary endpoint occurred in 43 patients in the vorapaxar group and in 70 patients in the placebo group (2-year Kaplan-Meier rates: 8.2 and 12.9%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vorapaxar loading dose of 40 mg and a daily maintenance dose of 2.5 mg thereafter vs placebo Either treatment in addition to physician-guided standard therapy	the TRACER trial undergoing CABG	Median follow-up period of 502 days	recurrent ischemia with rehospitalization, or urgent coronary revascularization; composite of moderate or severe bleeding according to the GUSTO classification and clinically significant bleeding according to the TIMI classification Secondary: Composite of death from CV causes, MI, or stroke	respectively), corresponding to a 45% reduction (adjusted HR: 0.55; 95% CI: 0.36 to 0.83; P=0.005). The CABG-related TIMI major bleeding was not a statistically significant difference between vorapaxar and placebo, although it was numerically higher with vorapaxar (HR: 1.36; 95% CI: 0.92 to 2.02; P=0.12), as it was for GUSTO severe bleeding related to CABG (HR: 1.35; 95% CI: 0.80 to 2.29; P=0.26). Secondary: Vorapaxar was also associated with lower occurrence of the key secondary endpoint (43 events; 2-year Kaplan-Meier rate of 8.2%) compared with placebo (58 events; 2-year Kaplan-Meier rate of 10.2%) in patients undergoing CABG (adjusted HR: 0.66; 95% CI: 0.43 to 1.01; P=0.057).
Mahaffey et al.[93] (2014) TRACER Vorapaxar loading dose of 40 mg and a daily maintenance dose of 2.5 mg thereafter vs placebo Either treatment in addition to physician-guided standard	Subgroup analysis of TRACER Patients enrolled in the TRACER trial stratified by aspirin dose (low, ≤100 mg; medium, >100 and <300 mg; high, ≥300 mg)	N=12,944 (7,523, 1,049, and 3,943 participants were treated with low-, medium-, and high-dose ASA at baseline, respectively) Median follow-up period of 502 days	Primary: Composite of death from CV causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization; composite of moderate or severe bleeding according to the GUSTO classification and clinically significant bleeding according	Primary: Participants treated with ≥300 mg ASA had higher event rates compared with participants treated with ≤100 mg ASA. There were no statistically significant interactions between vorapaxar effect and ASA dose. Compared with participants treated with ≤100 mg of ASA, participants treated with ≥300 mg ASA had similar GUSTO severe bleeding event rates and slightly higher TIMI major bleeding rates. There were no statistically significant interactions between study treatment effect on bleeding and ASA dose. The unadjusted and adjusted hazard ratios in participants treated with ≤100 versus ≥300 mg of ASA suggested a trend toward more prominent bleeding risk associated with vorapaxar compared with placebo. Secondary: There were no statistically significant interactions between vorapaxar effect and ASA dose.

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therapy			to the TIMI classification Secondary: Composite of death from CV causes, MI, or stroke	
Valgimigli et al.[94] (2014) TRACER Vorapaxar loading dose of 40 mg and a daily maintenance dose of 2.5 mg thereafter vs placebo Either treatment in addition to physician-guided standard therapy	Subgroup analysis of TRACER Patients enrolled in the TRACER trial who underwent PCI during the index hospitalization	N=12,944 (7,479 patients [57.8%] underwent PCI) Median follow-up period of 502 days	Primary: Composite of death from CV causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization; composite of moderate or severe bleeding according to the GUSTO classification and clinically significant bleeding according to the TIMI classification Secondary: Composite of death from CV causes, MI, or stroke	Primary: At 2 years after the index PCI, the primary efficacy end point occurred in 15.6% of patients who received vorapaxar and 16.7% of patients who received placebo (adjusted HR, 0.96; 95% CI, 0.84 to 1.09). The cumulative incidence of hemorrhage was overall increased with vorapaxar. The relative increase of intracranial hemorrhage with vorapaxar was lesser in patients undergoing PCI compared with those not undergoing PCI, with a borderline statistical significant interaction (P=0.073). Secondary: The secondary end point occurred in 10.6% of patients who received vorapaxar and 12.5% of patients who received placebo (adjusted HR, 0.90; 95% CI, 0.78 to 1.05).
Qamar et al.[95] (2020) TRA2^{o}P-TIMI 50 Vorapaxar 2.5 mg once daily	DB, MC, PC, RCT subanalysis from TRA2^{o}P-TIMI 50 Trial Patients with	N=6,136 3 years	Primary: Composite of death, MI, or stroke Composite of	Primary: At three years, vorapaxar as compared to placebo resulted in a reduction in death, MI, and stroke in the overall population of patients with PAD (9.9% vs 11.6%; HR, 0.85; 95% CI, 0.73 to 0.99; P=0.03). At three years, vorapaxar reduced major adverse limb events in the overall

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vs placebo	atherosclerotic vascular disease, including prior MI, stroke, or symptomatic PAD		hospitalization for acute leg injury, urgent peripheral revascularization, or major amputation Secondary: Safety	population of patients with PAD (2.9% vs 4.0%; HR, 0.70; 95% CI, 0.53 to 0.92; P=0.011) Secondary: At three years, vorapaxar significantly increased major bleeding by 39% (6.6% vs 4.9%; HR, 1.39; 95% CI, 1.12 to 1.71; P= 0.003)
Schüpke et al.[96] (2019) Ticagrelor 180 mg loading dose (90 mg twice daily maintenance) vs prasugrel 60 mg loading dose (10 mg once daily maintenance) prasugrel maintenance dose 5 mg once daily in patients ≥75 years of age or <60 kg	MC, OL, RCT Patients hospitalized for ACS for which invasive evaluation was planned	N=4018 12 months	Primary: Composite of death, MI, or stroke at one year Secondary: Safety, individual components of primary endpoint	Primary: Death, MI, or stroke at one year occurred in 184 (9.1%) versus 137 (6.9%) patients in the ticagrelor and prasugrel group respectively (HR, 1.36; 95% CI, 1.09 to 1.70; P=0.006). Secondary: After one year death from any cause occurred in 4.5% vs 3.7% patients (HR, 1.23; 95% CI, 0.91 to 1.68), MI occurred in 4.8% vs 3.0% patients (HR, 1.63; 95% CI, 1.18 to 2.25), and stroke was reported in 1.1% vs 1.0% (HR, 1.17; 95% CI, 0.63 to 2.15) for ticagrelor vs prasugrel groups, respectively. Major bleeding was observed 5.4% of patients in the ticagrelor group and 4.8% of patients in the prasugrel group (HR, 1.12; 95% CI, 0.83 to 1.51; P=0.46).
Gimbel et al.[97] (2020) POPular AGE Ticagrelor 180 mg loading dose (90 mg twice daily	MC, OL, RCT Patients ≥70 years of age with NSTE-ACS and randomized within 72 hours of admission	N=1002 5 years	Primary: Bleeding requiring medical intervention and net clinical benefit of all-cause death, MI, stroke, and	Primary: Major or minor bleeding occurred in 88 (18%) patients in the clopidogrel group vs 118 (24%) patients in the ticagrelor group (HR, 0.71, 95% CI, 0.54 to 0.94; P=0.02). The composite net clinical benefit outcome consisting of all-cause death, MI, stroke, major and minor bleeding after one year occurred in 139 (28%) patients receiving clopidogrel versus 161 (32%) patients receiving ticagrelor. The absolute risk difference for

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maintenance) vs prasugrel 60 mg loading dose (10 mg once daily maintenance) vs clopidogrel 300-600 mg loading dose (75 mg daily maintenance) Therapies continued for 12 months	Prasugrel was not prescribed to patients who have had a stroke or transient ischemic attack; therefore, if those patients were randomly assigned to ticagrelor or prasugrel they could be given only ticagrelor		major or minor bleeding Secondary: Individual components from composite primary outcome, CV death, and definite stent thrombosis	clopidogrel was -4% (95% CI, -10.0 to 1.4; P=0.03) for non-inferiority and 0.82 (95% CI, 0.66 to 1.03; P=0.11) for superiority. Secondary: Death of any cause occurred in 7% vs 7% patients (HR, 1.08; 95% CI, 0.68 to 1.72; P=0.72), CV death occurred in 4% vs 3% (HR, 1.19; 95% CI, 0.60 to 2.37; P=0.60), MI occurred in 8% vs 8% patients (HR, 1.00; 95% CI, 0.63 to 1.57; P=0.99), unstable angina occurred in 2% vs 2% patients (HR, 1.08; 95% CI, 0.46 to 2.55; P=0.83), and stroke was reported in 1% vs 2% (HR, 0.5; 95% CI, 0.17 to 1.46; P=0.2) for clopidogrel vs ticagrelor groups, respectively.
Valina et al.[98] (2020) Ticagrelor 180 mg loading dose (90 mg twice daily maintenance) vs prasugrel 60 mg loading dose (10 mg once daily maintenance) prasugrel maintenance dose 5 mg once daily in	Post hoc analysis of ISAR-REACT 5 Patients with NSTE-ACS presenting with chest discomfort suggestive of myocardial ischemia for ≥10 minutes at rest within 48 hours	N=2,365 12 months	Primary: Composite of death, MI, stroke Secondary: Safety and individual components of primary outcome	Primary: All-cause death, MI, and stroke, occurred in 101 (8.7%) patients receiving ticagrelor versus 73 (6.3%) patients receiving prasugrel (HR, 1.41; 95% CI, 1.04 to 1.90). Secondary: Incidences of all cause death 4.3% vs 3.0% (HR, 1.43; 95% CI, 0.93 to 2.21), MI 4.5% vs 3.2% (HR, 1.43; 95% CI, 0.94 to 2.19), and stroke 0.9% vs 0.9% (HR, 1.03; 95% CI, 0.44 to 2.37) for patients receiving ticagrelor vs prasugrel, respectively. The safety endpoint, major bleeding, occurred in 49 (5.2%) vs 41 (4.7%) patients taking ticagrelor vs prasugrel, respectively (HR, 1.09; 95% CI, 0.72 to 1.65; P=0.69).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patients ≥75 years of age or <60 kg				
Lahu et al.[99] (2021) Ticagrelor 180 mg loading dose (90 mg twice daily maintenance) vs prasugrel 60 mg loading dose (10 mg once daily maintenance) prasugrel maintenance dose 5 mg once daily in patients ≥75 years of age or <60 kg	MC, RC, pre-specified analysis of ISAR-REACT 5 Patients presenting with ACS categorized into 2 groups according to smoking status	N=4,001 12 months	Primary: Composite of death, MI, or stroke Secondary: Safety, individual components of primary outcome	Primary: Death, MI, or stroke at one year after randomization in smokers occurred in 47 (7.0%) patients in the ticagrelor group and 41 (6.2%) patients in the prasugrel group (HR, 1.15; 95% CI, 0.76 to 1.75; P=0.510). Death, MI, or stroke at one year after randomization in nonsmokers occurred in 133 (10.2%) patients in the ticagrelor group and 94 (7.2%) patients in the prasugrel group (HR, 1.44; 95% CI, 1.10 to 1.87; P=0.007). Death, MI, or stroke at one year after randomization occurred in 88 patients in the smokers group and 227 patients in the nonsmokers group (cumulative incidence 6.6% and 8.7%, respectively; HR, 0.76; 95% CI, 0.59 to 0.97; P=0.029). Secondary: Major bleeding occurred in 60 patients in the group of smokers and 112 patients in the group of nonsmokers (cumulative incidence accounting for competing risk 5.5% and 5.7%; HR, 0.98; 95% CI, 0.7 to 1.31; P=0.913). In smokers incidences of all cause death 3.9% vs 3.2% (HR, 1.22; 95% CI, 0.69 to 2.17; P=0.501), MI 3.4% vs 3.2% (HR, 1.12; 95% CI, 0.62 to 2.03; P=0.699), and stroke 1.2% vs 0.5% (HR, 2.60; 95% CI, 0.69 to 9.83; P=0.158) for patients receiving ticagrelor vs prasugrel, respectively. In nonsmokers incidences of all cause death 4.6% vs 3.8% (HR, 1.21; 95% CI, 0.83 to 1.77; P=0.314), MI 5.5% vs 3.0% (HR, 1.87; 95% CI, 1.26 to 2.76; P=0.002), and stroke 1.1% vs 1.2% (HR, 0.89; 95% CI, 0.44 to 1.83; P=0.758) for patients receiving ticagrelor vs prasugrel, respectively.
Song et al.[100] (2021) SMART-DATE and SMART-CHOICE	MC, OL, RCT Patients with ACS after coronary stenting	N=4,453 12 months	Primary: Major adverse cardiac and cerebrovascular events	Primary: At 12 months, the primary endpoint of the MACCE occurred in 25 (2.9%) patients in the P2Y12 inhibitor monotherapy group, 72 (3.2%) patients in the conventional DAPT group, and 49 (3.6%) in the aspirin monotherapy group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
300 mg of aspirin and a 300 or 600 mg clopidogrel loading dose then 100 mg aspirin + 75 mg clopidogrel once daily maintenance vs prasugrel 10 mg once daily vs ticagrelor 90 mg twice daily			Secondary: Individual components of primary outcome and safety	The number of major adverse cardiac and cerebrovascular events were 25 (2.9%), 72 (3.2%), and 49 (3.6%) for P2Y12 inhibitor, conventional DAPT therapy, and aspirin monotherapy, respectively; P=0.654. Secondary: The number of all-case death events were 12 (1.4%), 46 (2.1%), and 27 (2.0%) for P2Y12 inhibitor, conventional DAPT therapy, and aspirin monotherapy, respectively; P=0.474. The number of MI were eight (0.9%), 27 (1.2%), and 21 (2.1%) for P2Y12 inhibitor, conventional DAPT therapy, and aspirin monotherapy, respectively; P=0.050. The number of stroke events were six (0.7%), 12 (0.5%), and nine (0.7%) for P2Y12 inhibitor, conventional DAPT therapy, and aspirin monotherapy, respectively; P=0.836. The number of major bleeding events were 15 (1.7%), 70 (3.1%), and 33 (2.4%) for P2Y12 inhibitor, conventional DAPT therapy, and aspirin monotherapy, respectively; P=0.086.
Procedures and/or Surgery				
Silvain et al.[101] (2020) ALPHEUS Ticagrelor 180 mg loading dose (90 mg twice daily maintenance) vs clopidogrel 300 to 600 mg loading dose (75 mg daily maintenance) Therapies continued for 30 days	DB, MC, OL, RCT Patients with stable CAD with indication for PCI	N=1910 30 days	Primary: PCI-related myocardial injury within 48 hours of procedure Secondary: Composite of death, MI, stroke, or TIA; safety	Primary: At 48 hours myocardial infarction and major myocardial injury was observed in 334 (35%) versus 341 (36%) patients in the ticagrelor and clopidogrel group, respectively (95% CI, 0.80 to 1.17; P=0.75). Secondary: At 48 hours the composite endpoint of death, MI, stroke, or TIA was observed in 85 (9%) versus 80 (8%) patients in the ticagrelor and clopidogrel group, respectively (95% CI, 0.77 to 1.47; P=0.68). There were seven major bleeding episodes reported at 30 days with five (1%) patients in the ticagrelor group and two (<1%) in the clopidogrel group; P=0.29. Minor bleeding episodes at 30 days were reported in 105 (11%) and 71 (8%) patients in the ticagrelor and clopidogrel groups respectively; P=0.007.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hamilos et al.[102] (2021) MIRTOS Ticagrelor 180 mg loading dose (90 mg twice daily maintenance) vs clopidogrel 300 to 600 mg loading dose (75 mg daily maintenance)	DB, MC, OL, PG, PRO, RCT Patients < 75 years of age with STEMI eligible for thrombolysis	N=335 3 months	Primary: Difference in post-PCI corrected TIMI frame count Secondary: Bleeding events	Primary: The difference in post-PCI corrected TIMI frame count was 24.33 ± 17.35 for clopidogrel group and 28.33 ± 17.59 for ticagrelor group; P=0.10. Secondary: Major bleeding events were reported in two (1.2%) and one (0.6%) patient for the ticagrelor and clopidogrel group, respectively; P=0.99. Minor bleeding events were reported in nine (5.4%) and three (1.8%) patients for the ticagrelor and clopidogrel group, respectively; P=0.03.
Scirica et al.[103] (2019) clopidogrel 300 to 600 mg loading dose (75 mg daily maintenance) vs prasugrel 60 mg loading dose (10 mg once daily maintenance) During the maintenance phase, low-dose aspirin (75 to 162 mg) was recommended in addition to study	DB, MC, RCT Patients with ACS receiving PCI	N=12,844 6 months	Primary: CV deaths or MI directly related to PCI Stent-related deaths or MI classified as Academic Research Consortium definite or probable ST Spontaneous CV or MI not related to stent or PCI Secondary: Rate of STEMI compared to	Primary: Among the 1,306 first events, 606 (46%) were procedural, 186 (14%) stent-related, and 514 (39%) spontaneous. The rate of procedural MI or CV death was 4.4% in patients receiving prasugrel and 5.1% in patients receiving clopidogrel (HR, 0.87; 95% CI, 0.74 to 1.02; P=0.078). For stent-related events, the rates were 1.0% and 2.1% (HR, 0.47; 95% CI, 0.35 to 0.65; P<0.001), and for spontaneous events, 3.9% vs. 4.8% (HR, 0.80; 95% CI, 0.67 to 0.95; P=0.012). Secondary: The effect of prasugrel compared with clopidogrel by event type was consistent for STEMI and NSTEMI for all three event types (procedural STEMI 4.3% vs. 5.3%; HR, 0.80; 95% CI, 0.59 to 1.10; procedural NSTEMI 4.4% vs. 5.0%; HR, 0.89; 95% CI, 0.74 to 1.07; stent-related STEMI 1.4% vs. 2.7%; HR, 0.51; 95% CI, 0.31 to 0.85; stent-related NSTEMI 0.9% vs. 1.9%; HR, 0.46; 95% CI, 0.31 to 0.67; spontaneous STEMI 3.2% vs. 4.6%; HR, 0.70; 95% CI, 0.49 to 1.00; spontaneous NSTEMI 4.2% vs. 5.0%; HR, 0.84; 95% CI, 0.69 to 1.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
drug			NSTEMI for each primary outcome	
Marquis-Gravel et al.[104] (2020) clopidogrel 75 mg daily vs prasugrel 10 mg once daily prasugrel maintenance dose 5 mg once daily in patients ≥75 years of age or <60 kg	DB, PC, RCT subanalysis of TRILOGY ACS Patients with unstable angina or NSTEMI within 10 days not undergoing revascularization	N=9,326 12 months	Primary: Non-CABG related severe/life-threatening or moderate GUSTO bleeding and major or minor TIMI bleeding Secondary: Not reported	Primary: Overall, 158 (1.69%) patients experienced a severe/life-threatening or moderate GUSTO non-CABG bleeding event, including 107 bleeding events through 12 months, 133 through 18 months, and 147 through 24 months. A total of 174 (1.87%) patients experienced a major or minor TIMI non-CABG–related bleeding event, including 122 cumulative bleeding events through 12 months, 147 through 18 months, and 162 events through 24 months. In the clopidogrel group, 3406 patients and 1257 patients experienced low risk and high risk GUSTO and TIMI bleeding, respectively. In the prasugrel group, 3346 patients and 1317 patients experienced low risk and high risk GUSTO bleeding, respectively. Prasugrel vs clopidogrel low risk GUSTO log rank P=0.361 and high risk P=0.172. Prasugrel vs clopidogrel low risk TIMI log rank P=0.073 and high risk P=0.742. Secondary: Not reported
Mehran et al.[105] (2019) Ticagrelor 90 mg twice daily + aspirin 81 mg to 100 mg once daily vs ticagrelor 90 mg twice daily	DB, MC, OL, PC, RCT Patients who had PCI with at least one approved drug-eluding stent and discharged with a regimen of ticagrelor	N=7,119 12 months	Primary: First occurrence of BARC type 2, 3, or 5 bleeding Secondary: Death from any cause, MI, or stroke	Primary: BARC type 2, 3, or 5 bleeding occurred in 141 patients (4.0%) who received ticagrelor plus placebo, as compared with 250 patients (7.1%) who received ticagrelor plus aspirin (HR, 0.56; 95% CI, 0.45 to 0.68; P<0.001), for a difference in risk of −3.08 percentage points (95% CI, −4.15 to −2.01). Secondary: Death from any cause, nonfatal myocardial infarction, or nonfatal stroke occurred in 135 patients (3.9%) who received ticagrelor plus placebo and in 137 patients (3.9%) who received ticagrelor plus aspirin (HR, 0.99; 95% CI, 0.78 to 1.25), for a difference in risk of −0.06 percentage points (95% CI, −0.97 to 0.84)
Leon et al.[106] (1998) Aspirin 325 mg QD	MC, RCT Patients undergoing stent implantation	N=1,653 30 days	Primary: Composite of death, revascularization	Primary: The primary end point was observed in 38 patients: 3.6% assigned to aspirin alone, 2.7% assigned to aspirin plus warfarin and 0.5% assigned to aspirin plus ticlopidine (P=0.001 for the comparison of all three groups).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 325 mg QD and warfarin (dose adjusted to INR 2.0 to 2.5) vs aspirin 325 mg QD and ticlopidine 250 mg BID			of target lesion, angiographically evident thrombosis or MI within 30 days Secondary: Achievement of <50% residual stenosis without death or emergency bypass surgery, procedure-related MI, hematologic dyscrasias, hemorrhagic and vascular surgical complications	Secondary: Compared to aspirin alone, and aspirin plus warfarin, treatment with aspirin and ticlopidine resulted in a lower rate of stent thrombosis (P=0.001) following coronary stenting. Hemorrhagic complications occurred in 10 patients: 1.8% with aspirin alone, 6.2% with aspirin plus warfarin and 5.5% with aspirin plus ticlopidine (P<0.001 for the comparison of all three groups); the incidence of vascular surgical complications was 0.4, 2.0, and 2.0%, respectively (P=0.02). There were no significant differences in the incidence of neutropenia or thrombocytopenia among the three treatment groups and the overall incidence was 0.3%.
Ahn et al.[107] (2008) CIDES Aspirin 100 to 200 mg/day and cilostazol 200 mg/day vs aspirin 100 to 200 mg/day and clopidogrel 75 mg/day	MC, RCT Diabetic patients who underwent successful stenting	N=280 7.1 months (mean duration)	Primary: Change in luminal diameter Secondary: Rate of angiographic restenosis	Primary: The minimal luminal diameter at follow-up period for the aspirin and cilostazol group was 2.55 mm compared to 2.4 mm in the aspirin and clopidogrel group (P value not significant). Secondary: The rate of angiographic restenosis (stent plus 5-mm borders) was 9 (8.0%) in the aspirin and cilostazol group and 20 (16.1%) in the aspirin and clopidogrel group (P=0.041).
Lee et al.[108] (2008) DECLARE-	MC, PRO, RCT Diabetic patients	N=400 9 months	Primary: In-stent late loss at six months	Primary: At six months, the in-stent late loss was significantly lower in the triple therapy vs dual therapy group (0.25 vs 0.38 mm; P=0.025).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DIABETES Aspirin 200 mg/day and clopidogrel 300 mg loading dose, followed by 75 mg QD vs aspirin 200 mg/day, clopidogrel 300 mg loading dose, followed by 75 mg QD, and cilostazol 200 mg loading dose, followed by 100 mg BID	≥18 years of age undergoing drug-eluting stent implantation		Secondary: In-segment late loss and restenosis rate at six months; stent thrombosis, target vessel revascularization, major adverse cardiac events (death, MI, and target lesion revascularization) at nine months; safety	Secondary: At six months, the in-segment late loss (0.42 vs 0.53 mm; P=0.031) and restenosis (8.0 vs 15.6%; P=0.033) were significantly lower in the triple therapy vs dual therapy group. At nine months, there was no difference in the rate of stent thrombosis (0.0 vs 0.5%; P=0.999). Target vessel revascularization was lower in the triple therapy vs dual therapy group (3.5 vs 8.0%; P=0.053). At nine months, major adverse cardiac events tended to be lower in the triple therapy than in the dual therapy group (3.0 vs 7.0%; P=0.066). Drug discontinuation was more common in the triple therapy vs dual therapy group (14.5 vs 2.5%; P<0.001) with skin rash and gastrointestinal disturbance the most common reasons for termination of cilostazol.
Han et al.[109] (2009) Aspirin 300 mg QD for one month, followed by 100 mg QD and clopidogrel 300 to 600 mg loading dose, followed by 75 mg QD vs aspirin 300 mg QD for one month, followed by 100 mg QD, clopidogrel 300 to 600 mg loading	OL Patients aged 20 to 80 years admitted with ACS (unstable angina, NSTEMI, or STEMI) undergoing successful coronary stenting	N=1,212 12 months	Primary: Major adverse cardiac or cerebral event at one year (defined as the composite of cardiac death, nonfatal MI, stroke, or target vessel revascularization) Secondary: Bleeding events at one year	Primary: Triple-antiplatelet treatment was associated with a significantly lower incidence of the primary end points (10.3 vs 15.1%; P=0.011). The need for target vessel revascularization was similar between patients who received triple- and dual-antiplatelet treatment (7.9 vs 10.7%; P=0.10). Multivariate analysis showed that female patients and clinically or angiographically high-risk patients benefited more from the triple-antiplatelet treatment. Secondary: There were no significant differences between the two regimens in terms of the risks for major and minor bleeding.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose, followed by 75mg QD and cilostazol 100 mg BID				
Jeong et al.[110] (2009) *ACCEL-RESISTANCE* Aspirin 200 mg QD, clopidogrel 75 mg QD, and cilostazol 200 mg/day vs aspirin 200 mg QD and clopidogrel 150 mg QD	RCT Patients with high post-treatment platelet reactivity undergoing coronary stenting	N=60 30 days	Primary: Platelet function Secondary: Not reported	Primary: After 30 days, significantly fewer patients in the triple vs high maintenance dose group had high post-treatment platelet reactivity (3.3 vs 26.7%; P=0.012). Percent inhibitions of 5 µmol/l ADP-induced Agg_{max} and late platelet aggregation (Agg_{late}) were significantly greater in the triple vs high maintenance group (51.1±22.5 vs 28.0±18.5%; P<0.001, and 70.9±27.3 vs 45.3±23.4%; P<0.001, respectively). Percent inhibitions of 20 µmol/l ADP-induced Agg_{max} and Agg_{late} were consistently greater in the triple vs high maintenance dose group. Percent change of $P2Y_{12}$ reaction units demonstrated a higher antiplatelet effect in the triple vs high maintenance dose group (39.6±24.1 vs 23.1±29.9%; P=0.022). Secondary: Not reported
Watanabe et al.[111] (2019) STOPDAPT-2 One-month regimen (given between 30 and 59 days after PCI) were either aspirin 81 to 200 mg/d, and clopidogrel 75 mg/d, or aspirin 81 to 200 mg/d, and prasugrel 3.75 mg/d, at the	Adjudicator-blinded, MC, OL, RCT Patients undergoing PCI with a drug-eluting stent	N=3,009 12 months	Primary: Composite of cardiovascular death, MI, ischemic or hemorrhagic stroke, definite stent thrombosis, or major or minor bleeding at 12 months Secondary: Composite of	Primary: The primary endpoint occurred in 2.36% of patients in the monotherapy group and 3.70% in the dual therapy group (absolute difference, −1.34%; 95% CI, −2.57 to −0.11%; HR, 0.64; 95% CI, 0.42 to 0.98; P<0.001 for noninferiority; P=0.04 for superiority). Secondary: For the major secondary cardiovascular end point, monotherapy also met criteria for noninferiority to dual therapy (1.96 vs 2.51%; absolute difference, −0.55%; 95% CI, −1.62 to 0.52%; HR, 0.79; 95% CI, 0.49 to 1.29; P=0.005 for noninferiority; P=0.34 for superiority). For the major secondary bleeding end point, monotherapy was superior to dual therapy (0.41 vs 1.54%; absolute difference, −1.13%; 95% CI, −1.84

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
discretion of the attending physician At one month, patients were randomized to receive: Clopidogrel monotherapy vs clopidogrel with aspirin			cardiovascular death, MI, ischemic or hemorrhagic stroke, or definite stent thrombosis and the major secondary bleeding end point was major or minor bleeding	to −0.42%; HR, 0.26; 95% CI, 0.11 to 0.64; P=0.004).
Hahn et al.[112] (2019) SMART-CHOICE $P2Y_{12}$ inhibitor monotherapy group (aspirin plus a $P2Y_{12}$ inhibitor for three months and thereafter a $P2Y_{12}$ inhibitor alone) vs dual therapy group (aspirin plus a $P2Y_{12}$ inhibitor for at least 12 months)	MC, NI, OL, RCT Patients undergoing PCI with a drug-eluting stent	N=2,993 12 months	Primary: Major adverse cardiac and cerebrovascular events (a composite of all-cause death, MI, or stroke) Secondary: The components of the primary end point and bleeding	Primary: Cumulative rates of major adverse cardiac and cerebrovascular events at 12 months were 2.9% for the $P2Y_{12}$ inhibitor monotherapy group and 2.5% for the dual therapy group (difference, 0.4%; 1-sided 95% CI, –∞% to 1.3%; P=0.007 for noninferiority), meeting criteria for noninferiority of $P2Y_{12}$ inhibitor monotherapy to dual therapy. Secondary: There were no significant differences in the cumulative rates of the components of the primary end point at 12 months for all-cause death, MI, and stroke. The risk of stent thrombosis was not significantly different between the two groups. The rate of bleeding was significantly lower in the $P2Y_{12}$ inhibitor monotherapy group than in the dual therapy group (2.0% vs 3.4%; HR, 0.58; 95% CI, 0.36 to 0.92; P=0.02). There was no significant difference in the risk of bleeding between the groups in the post hoc three-month landmark analysis (HR, 0.59; 95% CI, 0.34 to 1.01; P=0.053). The rate of major bleeding did not differ significantly between the two groups.
Hahn et al.[113] (2018) SMART-DATE	MC, NI, OL, RCT Patients with unstable angina,	N=2,993 18 months	Primary: Composite of all-cause death, MI, or stroke	Primary: Cumulative rates of major adverse cardiac and cerebrovascular events at 18 months were 4.7% for the 6-month group and 4.2% for the 12-month or longer group. The non-inferiority of the 6-month group to 12-month or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
6-month dual therapy group (aspirin plus a $P2Y_{12}$ inhibitor for six months and thereafter aspirin alone) vs 12-month or longer dual therapy group (aspirin plus a $P2Y_{12}$ inhibitor for at least 12 months	non-ST-segment elevation MI, or ST-segment elevation MI, undergoing PCI		Secondary: The individual components of the primary endpoint; definite or probable stent thrombosis as; and type 2 to 5 bleeding	longer group was met (absolute risk difference, 0.5%; upper limit of one-sided 95% CI, 1.8%; $p_{non\text{-}inferiority}$=0.03 with a predefined non-inferiority margin of 2.0%). Secondary: Although all-cause mortality did not differ significantly between the two groups at 18 months (2.6% vs 2.9%; HR, 0.90; 95% CI, 0.57 to 1.42; P=0.90), MI occurred more frequently in the 6-month group than in the 12-month or longer group (1.8% vs 0.8%; HR, 2.41; 95% CI, 1.15 to 5.05; P=0.02). The risk of stent thrombosis and of stroke did not differ significantly between the two groups (P=0.32 and P=0.84). The rate of type 2 to 5 bleeding also did not differ significantly between the two groups (P=0.09).
Vranckx et al.[114] (2018) GLOBAL LEADERS Aspirin 75 to 100 mg daily plus ticagrelor 90 mg twice daily for one month, followed by 23 months of ticagrelor monotherapy (experimental group) vs standard dual antiplatelet therapy with aspirin 75 to 100 mg daily plus either clopidogrel 75 mg daily (for patients with stable coronary	MC, OL, RCT Patients undergoing PCI with a drug-eluting stent	N=15,968 2 years	Primary: Composite of all-cause mortality or non-fatal centrally adjudicated new Q-wave MI Secondary: Grade 3 or 5 bleeding	Primary: At two-year follow-up, a primary endpoint event had occurred in 3.81% of participants in the experimental group and 4.37% in the standard group (rate ratio, 0.87; 95% CI, 0.75 to 1.01; P=0.073). Secondary: Grade 3 or 5 bleeding occurred in 163 participants in the experimental group and 169 in the standard group (2.04% vs 2.12%; rate ratio, 0.97; 95% CI, 0.78 to 1.20; P=0.77).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
artery disease) or ticagrelor 90 mg twice daily (for patients with acute coronary syndromes) for 12 months, followed by aspirin monotherapy for 12 months (standard group)				
Mehta et al.[115] (2001) PCI-CURE Aspirin and clopidogrel or placebo prior to PCI; after PCI, stented patients received OL clopidogrel or ticlopidine in combination with aspirin for two to four weeks; then clopidogrel or placebo was resumed (for 3 two 12 months after initial randomization)	DB, RCT Patients with non-ST-elevation ACS from the CURE study undergoing PCI	N=2,658 Average duration of follow-up after PCI was eight months	Primary: Composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days of PCI (main primary end point); cardiovascular death or MI from time of PCI to scheduled end of trial Secondary: Not reported	Primary: A total of 4.5% of patients in the clopidogrel and aspirin group reached the primary end point compared to 6.4% in the aspirin group (P=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI, or any revascularization (P=0.03) and of cardiovascular death or MI (P=0.047). Overall, clopidogrel was associated with a 31% reduction in cardiovascular death or MI, including events before and after PCI (P=0.002). At follow-up, there was no significant difference in major bleeding between the groups (P=0.64). Secondary: Not reported
Takeyasu et al.[116] (2005) Cilostazol 200 mg/day and aspirin 81 to 200 mg/day vs	OL, RCT Patients with ischemic heart disease receiving stents	N=642 6 months	Primary: Rate of stenosis according to qualitative coronary angiography analysis of minimal lumen	Primary: The rates of restenosis (27.8 vs 29.3%; P value not significant) and target lesion revascularization (22.4 vs 23.5%; P value not significant) were similar between patients receiving cilostazol and ticlopidine. The rate of subacute thrombosis was significantly greater with cilostazol than ticlopidine (2.5 vs 0.3%; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ticlopidine 200 mg/day and aspirin 81 to 200 mg/day			diameter of artery, safety Secondary: Not reported	There were no differences in the incidence of adverse reactions with the exception of purpura, which was reported more frequently with ticlopidine than cilostazol (1.0 vs 0.0%; P=0.045). Secondary: Not reported
Sabatine et al.[117] (2005) PCI-CLARITY Clopidogrel (300 mg loading dose, followed by 75 mg QD) plus aspirin (150 to 325 mg on the first day, followed by 75 to 162 mg QD) vs placebo plus aspirin (150 to 325 mg on the first day, followed by 75 to 162 mg QD)	DB, MC, PC, RCT Patients with STEMI who received fibrinolytics and underwent PCI (after mandated angiography in CLARITY-TIMI 28)	N=1,863 30 days	Primary: Composite of cardiovascular death, recurrent MI or stroke from PCI to 30 days after randomization Secondary: MI or stroke before PCI and the primary end point from randomization to 30 days	Primary: Pretreatment with clopidogrel in patients receiving concurrent aspirin significantly reduced the primary end point following PCI compared to aspirin alone (3.6 vs 6.2%; adjusted OR, 0.54; 95% CI, 0.35 to 0.85; P=0.008). Pretreatment with clopidogrel and aspirin also reduced the incidence of MI or stroke prior to PCI (4.0 vs 6.2%; OR, 0.62; 95% CI, 0.40 to 0.95; P=0.03). Secondary: Overall, pretreatment with clopidogrel significantly reduced the secondary outcome (7.5 vs 12.0%; adjusted OR, 0.59; 95% CI, 0.43 to 0.81; P=0.001). There was no significant excess in the rates of major or minor bleeding in patients receiving dual therapy vs aspirin alone (2.0 vs 1.9%, respectively; P>0.99).
Steinhubl et al.[118] (2002) CREDO Clopidogrel 300 mg loading dose (3 to 24 hours before PCI), then clopidogrel 75 mg QD through 12 months vs	DB, MC, PC, RCT Patients undergoing PCI	N=2,116 12 months	Primary: One-year incidence of the composite of death, MI, or stroke; 28-day incidence of the composite of death, MI or urgent target vessel revascularization Secondary:	Primary: Long-term (one year) clopidogrel and aspirin therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke vs aspirin alone (95% CI, 3.9 to 44.4; P=0.02; absolute reduction, 3%). Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI or urgent revascularization at 28 days (-18.5%; 95% CI, -14.2 to 41.8; P=0.23). Secondary: A similar level of benefit was found in the individual components of the primary end point at one year, although individual outcomes were not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo (3 to 24 hours before PCI), then clopidogrel 75 mg QD through day 28, then placebo through 12 months All patients received aspirin 325 mg prior to PCI, then 325 mg QD through day 28, then 81m to 325 mg QD thereafter.			Components of composite end points, administration of clopidogrel <6 hours or ≥6 hours before PCI, need for target vessel revascularization or any revascularization at one year	significant. Treatment randomization did not appear to influence the rate of target vessel revascularization or any other revascularization during the follow-up period. In a prespecified subgroup analysis, patients who had received clopidogrel at least six hours before PCI experienced a reduction in the relative combined risk of death, MI, or stroke by 38.6% (95% CI, -1.6 to 62.9; P=0.051) compared to no reduction when treatment was given less than six hours before PCI (P=0.051). Risk of major bleeding at one year increased, but not significantly (8.8% with clopidogrel vs 6.7% with aspirin alone; P=0.07).
Lev et al.[119] (2008) Clopidogrel 300 to 600 mg before PCI vs clopidogrel 300 to 600 mg immediately after PCI Patients were treated with aspirin before PCI, then aspirin and clopidogrel 75 mg QD for 3 to 12 months after PCI	PRO Patients with chest pain and STEMI undergoing emergency PCI	N=292 6 months	Primary: Occurrence of TIMI myocardial perfusion grade 3 after PCI Secondary: Incidence of reinfarction, stent thrombosis, target vessel revascularization, death	Primary: TIMI myocardial perfusion grade 3 occurred in a higher proportion of patients in the clopidogrel pretreatment group than in the no pretreatment group (85 vs 71%; P=0.01). Secondary: The incidence of reinfarction at 30 days (0.0 vs 3.2%, respectively; P=0.04) and six months (0.6 and 3.9%, respectively; P=0.09) was lower in the pretreatment group than in the no pretreatment group. The incidence of stent thrombosis at 30 days (0.0 vs 2.4%, respectively; P=0.08) and six months (0.0 and 3.9%, respectively; P=0.02) was lower in the pretreatment group than in the no pretreatment group. The incidence of death and target vessel revascularization were not significantly different between the two treatment groups at 30 days (P=0.6 and P=1.0) or six months (P=0.7 and P=0.9).
Banerjee et al.[120] (2008) Clopidogrel for ≥1 year following PCI	RETRO Patients who underwent PCI	N=530 2.4±0.8 years (mean follow-up)	Primary: All cause mortality Secondary: Incidence of major	Primary: Twelve (3.5%) patients who received clopidogrel for ≥1 year died compared to 28 (15%) patients who received clopidogrel for <1 year (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clopidogrel for <1 year following PCI Patients were free of cardiovascular events for six months after PCI, and had follow-up available for >12 months.			adverse cardiovascular events (composite of all cause death, nonfatal MI and repeat coronary revascularization by PCI or CABG)	On a multivariate analysis, the use of clopidogrel for ≥1 year was associated with lower mortality (HR, 0.28; 95% CI, 0.14 to 0.59; P<0.001), independent of traditional cardiovascular risk factors, clinical presentation and drug eluting stent use. Survival in the <1 and ≥1 year clopidogrel groups was 97 and 99%, respectively, at two years after PCI, and 80 and 93%, respectively, at three years after PCI. Secondary: There were no significant differences in the incidence of nonfatal MI (P=0.50), repeat coronary revascularization (P=0.16) or major adverse cardiovascular events between the two groups (P=0.10). Patients who experienced major adverse cardiovascular events were significantly older and had preexisting CAD, and those who died were more likely to have chronic renal disease and heart failure.
Han et al.[121] (2009) Clopidogrel 600 mg once, followed by 75 mg/day vs clopidogrel 600 mg once, followed by 150 mg/day All patients received aspirin 300 mg/day. All patients received dual antiplatelet therapy on admission followed by maintenance dose	RCT Patients ≥18 years of age, diagnosed with ACS, planned pretreatment with 600 mg clopidogrel loading dose, presence of ≥1 severe coronary stenosis requiring PCI located in native arteries and suitable for drug eluting stent implantation	N=813 30 days	Primary: Major adverse cardiac event (composite of cardiac death, nonfatal MI and urgent target vessel revascularization) Secondary: Stent thrombosis, major and minor bleeding events	Primary: A total of 13 patients reached the primary end points, including four (1.0%) patients in the 150 mg group and nine (2.2%) patients in the 75 mg group (P>0.05). There was no significant difference in cumulative major adverse cardiac event-free survival between the two groups. The incidences of MI (two vs five; P>0.05), urgent target vessel revascularization (three vs eight; P>0.05) and cardiac death (one vs one; P>0.05) were similar between the two groups. Secondary: The incidence of stent thrombosis (zero vs six; P<0.05) was significantly lower in the 150 mg group compared to the 75 mg group. There was no significant differences between both groups regarding the risk of major (one vs zero; P>0.05) or minor (two vs one; P>0.05) bleedings.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
administration according to study protocol and PCI was performed within 48 hours of admission.				
Valgimigli et al.[122] (2012) PRODIGY Clopidogrel 300 or 600 mg once, followed by 75 mg/day plus aspirin 160 to 325 mg orally or 500 mg intravenously once, followed by 80 to 160 mg/day for six months vs clopidogrel 300 or 600 mg once, followed by 75 mg/day plus aspirin 160 to 325 mg orally or 500 mg intravenously once, followed by 80 to 160 mg/day for 24 months Patients in the six-month group who received bare metal stent were allowed to	MC, OL, RCT Patients ≥18 years of age with chronic stable CAD, NSTEMI or STEMI ACS who were receiving a stent placement	N=2,013 24 months	Primary: Composite of death of any cause, nonfatal MI and cerebrovascular accident Secondary: Components of the composite primary endpoint, cardiovascular death, stent thrombosis and bleeding outcomes	Primary: The cumulative risk of the primary endpoint at 24 months was 10.1% in the 24- month group and 10.0% in the six-month group (HR, 0.98; 95% CI, 0.74 to 1.29; P=0.91). Secondary: When individual components were analyzed separately, there were no differences between the six-month and 24-month groups with regard to risks of death of any cause (6.6% for both; HR, 1.00; 95% CI, 0.72 to 1.40; P=0.98), nonfatal MI (4.2 vs 4.0%; HR, 1.06; 95% CI, 0.69 to 1.63; P=0.80), cerebrovascular accident (1.4 vs 2.1%; HR, 0.60; 95% CI, 0.29 to 1.23; P=0.17), cardiovascular death (3.8 vs 3.7%; HR, 1.03; 95% CI, 0.66 to 1.61; P=0.89) and stent thrombosis (4.7 vs 3.9%; HR, 1.21; 95% CI, 0.79 to 1.86; P=0.38). Safety end point was a composite end point of fatal bleeding, overt bleeding plus hemoglobin drop of ≥3 g/dL, bleeding that requires nonsurgical/medical intervention, bleeding that leads to hospitalization or increased level of care and bleeding that prompts evaluation. Dual-antiplatelet therapy for six months was associated with a lower risk of bleeding compared to the 24-month therapy (3.5 vs 7.4%; HR, 0.46; 95% CI, 0.31 to 0.69; P=0.00018).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
discontinue treatment after 30 days.				
Gwon et al.[123] (2012) EXCELLENT Clopidogrel 75 mg/day plus aspirin 100 to 200 mg/day for six months then aspirin alone for six months vs clopidogrel 75 mg/day plus aspirin 100 to 200 mg/day for 12 months All patients received aspirin ≥300 mg plus clopidogrel 300 to 600 mg once before PCI.	MC, OL, PRO, RCT Korean patients with coronary vessel occlusion and who were undergoing PCI with drug-eluting stent placement	N=1,443 12 months	Primary: Target vessel failure defined as a composite of cardiac death, MI and target vessel revascularization Secondary: Components of the composite primary endpoint, death of any cause, death or MI, stent thrombosis, major bleeding according to TIMI criteria, major adverse cardiocerebral events and composite safety endpoint	Primary: Incidence of target vessel failure was similar between the six- and 12-month dual antiplatelet treatment groups (4.8 vs 4.3%; HR, 1.14; 95% CI, 0.70 to 1.86). In the pre-specified subgroup analysis, the incidence of target vessel failure was higher with the six-month group compared to the 12-month group for patients with diabetes (HR, 3.16; 95% CI, 1.42 to 7.03). Secondary: No differences were seen between the six- and 12-month groups in the rate of cardiac death (0.3 vs 0.4%; HR, 0.67; 95% CI, 0.11 to 3.99), MI (1.8 vs 1.0%; HR, 1.86; 95% CI, 0.74 to 4.67) and target vessel revascularization (3.1 vs 3.2%; HR, 2.00; 95% CI, 0.75 to 5.34). Risk of death of any cause was 0.6 and 1.0% in the six-month and 12-month groups (HR, 0.57; 95% CI, 0.17 to 1.95). Death or MI occurred in 2.4 and 1.9% of patients in the six- and 12-month groups (HR, 1.21; 95% CI, 0.60 to 2.47). Incidence of stent thrombosis was higher with the six-month group but was not statistically different from the 12-month group (0.9 vs 0.1%; HR, 6.02; 95% CI, 0.72 to 49.96). Risk of TIMI major bleeding was similar between the six- and 12-month groups (0.3 vs 0.6%; HR, 0.5; 95% CI, 0.09 to 2.73). Risk of major cardiocerebral event, which is a composite of death, MI, stroke, stent thrombosis and any revascularization, was similar between the six- and 12-month groups (8.0 vs 8.5%; HR, 0.94; 95% CI, 0.65 to 1.35). Safety endpoint, defined as a composite of death, MI, stroke, stent thrombosis and TIMI major bleeding, was also similar between the six- and 12-month groups (3.3 vs 3.0%; HR, 1.15; 95% CI, 0.64 to 2.06).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CURRENT-OASIS 7.[124] (2010) Clopidogrel 600 mg once, followed by 150 mg/day for six days, followed by clopidogrel 75 mg/day through day 30 (double dose) vs clopidogrel 300 mg once, followed by 75 mg/day for six days, followed by 75 mg/day through day 30 (standard dose) and aspirin ≥300 mg/day once, followed by 75 to 100 mg/day through day 30 (low-dose) vs aspirin ≥300 mg/day once, followed by 300 to 325 mg/day through day 30 (high-dose)	2x2 factorial design, RCT Patients ≥18 years of age who presented with a NSTE ACS or a STEMI	N=25,086 (n=17,263 underwent PCI) 30 days	Primary: Composite of cardiovascular death, MI or stroke Secondary: Composite of death from cardiovascular causes, MI, stroke or recurrent ischemia; the individual components of the primary endpoint; death from any cause; bleeding	Primary: The primary outcome occurred in 4.2% of patients in the double-dose group compared to 4.4% with the standard dose group (HR, 0.94; 95% CI, 0.83 to 1.06; P=0.30). Overall, 4.2% of the patients in the high-dose aspirin group had a primary outcome event compared to 4.4% of patients in the low-dose aspirin group (HR, 0.97; 95% CI, 0.86 to 1.09; P=0.61). A nominally significant interaction between the clopidogrel dose comparison and the aspirin dose comparison for the primary outcome was noted (P=0.04). Among patients assigned to high-dose aspirin, the primary outcome occurred in 3.8 and 4.6% in the double and standard clopidogrel dose groups (HR, 0.82; 95% CI, 0.69 to 0.98; P=0.03). Among patients assigned to low-dose aspirin, there was no significant difference between the double and standard clopidogrel groups (4.5 vs 4.2%; HR, 1.07; 95% CI, 0.90 to 1.26; P=0.46). Secondary: Consistent results were observed for each component of the primary outcome, as well as for the expanded composite endpoint for the clopidogrel and aspirin dose comparison. A nominally significant reduction in recurrent ischemia alone was associated with high-dose aspirin as compared to low-dose aspirin (0.3 vs 0.5%; HR, 0.63; 95% CI, 0.43 to 0.94; P=0.02). The rate of death from any cause did not differ significantly between the double and standard dose groups (2.3 vs 2.4%; HR with the double dose, 0.96; 95% CI, 0.82 to 1.13; P=0.61). Death from any cause occurred in 2.2 and 2.5% of patients in the high- and low-dose groups (HR, 0.87; 95% CI, 0.74 to 1.03; P=0.10). Major bleeding occurred in 2.5 and 2.0% of patients in the double and standard dose groups (HR, 1.24; 95% CI, 1.05 to 1.46; P=0.01). The aspirin groups did not differ significantly with respect to major bleeding (P value not reported). There was a nominally significant increase in the increase of minor bleeding among patients who received high-dose aspirin (HR, 1.13; 95% CI, 1.00 to 1.27; P=0.04). There was a small increase in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were to undergo early angiography and PCI, if appropriate, no later than 72 hours after randomization.				the incidence of major gastrointestinal bleeding among patients who received high-dose aspirin, as compared to those who received low-dose aspirin (0.4 vs 0.2%; P=0.04).
Bertrand et al.[125] (2000) CLASSICS Clopidogrel 300 mg loading dose, followed by 75 mg QD and aspirin 325 mg QD vs clopidogrel 75 mg QD and aspirin 325 mg QD vs ticlopidine 250 mg BID and aspirin 325 mg QD	RCT Patients receiving a stent placement	N=1,020 28 days	Primary: Major peripheral or bleeding complications, neutropenia, thrombocytopenia or early discontinuation due to noncardiac adverse event Secondary: Incidence of cardiac events	Primary: Primary end point occurred in 4.6% of patients in the combined clopidogrel group and in 9.1% of patients in the ticlopidine group (RR, 0.50; 95% CI, 0.31 to 0.81; P=0.005). Secondary: Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups (1.2% with clopidogrel loading dose, 1.5% with clopidogrel without the loading dose and 0.9% with ticlopidine; P value not significant for all comparisons).
Isshiki et al.[126] (2012) CLEAN Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 81 to 100 mg/day vs	DB, MC, RCT Japanese patients ≥20 years of with stable angina or history of MI and who were undergoing PCI	N=931 12 weeks	Primary: Composite of clinically significant bleeding, blood disorders, elevated liver function tests and study drug discontinuation due to an adverse	Primary: The composite primary endpoint occurred in 10.1% of patients in the clopidogrel group and 34.2% in the ticlopidine group (HR, 0.259; 95% CI, 0.187 to 0.359; P<0.0001). When individual components were analyzed separately, there were no differences between clopidogrel and ticlopidine with regard to the risks of clinically significant bleeding (0.9 vs 0.6%; HR, 1.328; 95% CI, 0.297 to 5.936) and blood disorder (1.7 vs 3.4%; HR, 0.495; 95% CI, 0.212 to 1.158). Clopidogrel was associated with lower risk of liver function test

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ticlopidine 100 mg BID plus aspirin 81 to 100 mg/day			reaction Secondary: Composite of all-cause mortality, acute MI, revascularization, stent thrombosis or ischemic stroke	elevation (6.0 vs 30.3%; HR, 0.172; 95% CI, 0.115 to 0.258) and treatment discontinuation due to an adverse reaction (3.9 vs 13.1%; HR, 0.281; 95% CI, 0.166 to 0.476) compared to ticlopidine. Secondary: There was no difference in the cumulative risk of the composite cardiovascular endpoint between the clopidogrel and ticlopidine groups (9.2 vs 10.3%; HR, 0.886; 95% CI, 0.587 to 1.337). Acute MI was reported in 7.7 and 9.2% of patients in the clopidogrel and ticlopidine groups, revascularization in 1.5 and 0.4% of patients and ischemic stroke in 0.2 and 0.6% of patients in the respective treatment group (P values not reported). No death or stent thrombosis was reported during the study.
Gao et al.[127] (2009) Clopidogrel 75 mg/day and aspirin 100 mg/day vs clopidogrel 75 mg/day	RCT Patients undergoing elective CABG	N=197 12 months	Primary: CABG graft patency rates Secondary: Not reported	Primary: At one month and 12 months after CABG graft patency rates of clopidogrel monotherapy group were, respectively, 99.0 and 96.9% for the left internal mammary artery, and 98.1 and 93.5% for the saphenous vein grafts. Those of the dual antiplatelet therapy group were, respectively, 98.9 and 97.8% for left internal mammary artery, and 98.2 and 96.3% for saphenous vein grafts. Thus, there were no significant differences in graft patency between the two groups (P>0.05). Secondary: Not reported
Park et al.[128] (2010) Clopidogrel 75 mg/day and aspirin (100 to 200 mg/day) vs aspirin 100 to 200 mg/day	OL Patients who had undergone drug eluting stent implantation ≥12 months prior to enrollment, who had not had a major cardiovascular event, or major bleeding since	N=2,701 19.2 months (mean duration)	Primary: First occurrence of MI or death from cardiac causes after assignment to a treatment group Secondary: Death from any cause	Primary: The cumulative risk of the primary outcome at two years was 1.8% with dual *antiplatelet* therapy, as compared to 1.2% with aspirin monotherapy (HR, 1.65; 95% CI, 0.80 to 3.36; P=0.17). Secondary: There was no significant difference between the two treatment groups in the risk of individual secondary end points. In the dual antiplatelet therapy group as compared to the aspirin-monotherapy group, there was a nonsignificant increase in the composite risk of myocardial infarction, stroke, or death from any cause (HR, 1.73; 95% CI, 0.99 to 3.00; P=0.051) and in the composite risk of myocardial infarction, stroke, or death from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	implantation			cardiac causes (HR, 1.84; 95% CI, 0.99 to 3.45; P=0.06).
Sibbing et al.[129] (2009) Clopidogrel 75 mg/day vs pantoprazole vs omeprazole vs esomeprazole	CS, OB Patients on maintenance clopidogrel therapy scheduled for a coronary angiography who were also taking a PPI at the time point of platelet function testing	N=1,000 Duration varied	Primary: Platelet aggregation in patients treated with pantoprazole Secondary: Platelet aggregation in patients treated with omeprazole or esomeprazole	Primary: Those treated with pantoprazole (P=0.88) had similar platelet aggregation compared to those not treated with a PPI. Secondary: Those treated with omeprazole experienced significantly higher platelet aggregation compared to patients without PPI treatment (P=0.001). Those treated with esomeprazole (P=0.69) had similar platelet aggregation compared to those not treated with a PPI.
Trenk et al.[130] (2012) TRIGGER-PCI Prasugrel 60 mg loading dose followed by 10 mg/day vs clopidogrel 75 mg/day All patients received clopidogrel 600 mg loading dose plus aspirin ≥250 mg within 24 hours	RCT Patients 18 to 80 years of age with stable CAD who underwent PCI with at least one drug-eluting stent placement and demonstrated high on-treatment platelet reactivity after clopidogrel loading dose followed by one-time clopidogrel 75 mg	N=423 6 months	Primary: Composite of cardiovascular death and MI and non-CABG-related TIMI major bleeding Secondary: Composite of cardiovascular death, MI and target vessel revascularization, composite of cardiovascular death, MI, stroke and rehospitalization	Primary: Composite primary endpoint occurred in one patient in the clopidogrel group vs none in the prasugrel group (P>0.05). Non-CABG-related TIMI major bleeding occurred in three patients in the prasugrel group and one in the clopidogrel group (P>0.05). Secondary: Composite endpoint of cardiovascular death, MI and revascularization occurred in two patients in each treatment group (P>0.05). Composite endpoint of cardiovascular death, MI, stroke and rehospitalization for cardiac ischemic event occurred in two patients treated with prasugrel and six patients treatment with clopidogrel (HR, 0.493; 95% CI, 0.090 to 2.692). Secondary safety endpoint, a composite of any non-CABG-related bleeding, occurred in 2.9 and 1.9% in the prasugrel and clopidogrel groups, respectively (HR, 1.517; 95% CI, 0.428 to 5.376).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
before PCI and one-time clopidogrel 75 mg the morning after PCI.			for cardiac ischemic event and composite safety endpoint	The authors concluded that due to low event rate, the utility of prasugrel in patients with high on-treatment platelet reactivity could not be determined.
Wiviott et al.[9] (2007) Prasugrel 60 mg loading dose, followed by 10 mg/day vs clopidogrel 600 mg loading dose, followed by 150 mg/day Maintenance dose administered upon PCI completion.	AC, DB, DD, RCT, XO Patients ≥18 years of age, who were scheduled to undergo cardiac catheterization with planned PCI for angina and ≥1 of the following: angiograph within 14 days with ≥1 PCI amendable legion, objective findings of ischemia within eight weeks of study, or prior PCI or CABG	N=201 28 days (treatment periods were 14 days each)	Primary: Inhibition of platelet aggregation with 20 μmol/L adenosine diphosphate at six hours during the loading dose phase and at 14±2 days of the maintenance dose Secondary: Mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate, mean $P2Y_{12}$ assay percent inhibition, safety	Primary: For the loading dose phase, mean inhibition of platelet aggregation with 20 μmol/L adenosine diphosphate at six hours was significantly greater (higher inhibition of platelet aggregation indication of greater antiplatelet effect) in the prasugrel group (74.8%) compared to the clopidogrel group (31.8%). The mean difference between the two groups was 43.2% (P<0.0001). For the maintenance dose phase mean inhibition of platelet aggregation with 20 μmol/L adenosine diphosphate at 14±2 days was significantly greater in the prasugrel group (61.3%) compared to the clopidogrel group (46.1%). The mean difference between the two groups was 14.9% (P<0.0001). Secondary: For the loading dose phase mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate was significantly lower (lower maximal platelet aggregation indication of greater antiplatelet effect) in the prasugrel group (18.9%) compared to the clopidogrel group (52.1%). The mean difference between the two groups was 33.1% (P<0.0001). For the maintenance dose phase mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate at 14±2 days was significantly lower in the prasugrel group (29.2%) compared to the clopidogrel group (40.9%). The mean difference between the two groups was 11.3% (P<0.0001). For the loading dose phase prasugrel also showed significantly greater platelet inhibition with the $P2Y_{12}$ assay (89.5%) compared to clopidogrel (38.4%). The mean difference between the two groups was 51.4% (P<0.0001). For the maintenance dose phase prasugrel also showed significantly greater platelet inhibition with the $P2Y_{12}$ assay (83.3%) compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				clopidogrel (65.1%). The mean difference between the two groups was 18.9% (P<0.0001). There were no TIMI major bleeding episodes in either treatment group. For TIMI minor bleeding episodes 2% of patients in the prasugrel group experienced a minor bleed compared to 0% in the clopidogrel group. In the prasugrel group 18.6% of the patients reported a hemorrhagic event whether minor or major, compared to 14.1% in the clopidogrel group, however the difference was not significant (P value not reported).
Motovska et al.[131] (2018) PRAGUE-18 Prasugrel vs ticagrelor	MC, OL, RCT Patients with acute MI treated with PCI	N=1,230 12 months	Primary: Composite of cardiovascular death, MI, or stroke Secondary: Components of the primary endpoint, bleeding	Primary: The incidence of the key composite efficacy endpoint was 6.6% in the prasugrel group compared with 5.7% in the ticagrelor group (HR, 1.167; 95% CI, 0.742 to 1.835; P=0.503). Secondary: There were no significant differences in rates of cardiovascular death (3.3% vs 3.0%; P=0.769), nonfatal MI (3.0% vs 2.5%; P=0.611), stroke (1.1% vs 0.7%; P=0.423), all-cause death (4.7% vs 4.2%; P=0.654), and definite stent thrombosis (1.1% vs 1.5%; P=0.535). Bleeding events occurred in 10.9% of patients in the prasugrel group and in 11.1% in the ticagrelor group (HR, 0.985; 95% CI, 0.703 to 1.381; P=0.930). There was no significant difference in the rate of major bleeding as defined by TIMI (0.9% vs 0.7%; P=0.754) and Bleeding Academic Research Consortium (2.4% vs 1.5%; P=0.308) criteria.
Peripheral Artery Disease				
Hiatt et al.[132] (2008) CASTLE Cilostazol 50 to 100 mg BID vs placebo	DB, MC, PA, PC, RCT Patients ≥17 years with a clinical diagnosis of PAD and symptoms of claudication	N=1,435 Up to 3.5 years	Primary: All-cause mortality on treatment (defined as period while taking the study drug and for 30 days after discontinuing therapy)	Primary: Long-term adherence to cilostazol was poor with >60% of participants discontinuing therapy by 36 months. There were 18 deaths in patients receiving cilostazol (N=717) and 19 deaths in patients receiving placebo (N=718) (HR, 0.99; 95% CI, 0.52 to 1.88). The study was underpowered to meet its primary end point. In the full ITT population at 36 months, there were 49 deaths for cilostazol patients and 52 deaths for placebo patients (HR, 0.94; 95% CI, 0.64 to 1.39). Thus most deaths occurred >30 days after study drug

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Safety	discontinuation. The incidence of cardiovascular deaths was similar between the two treatment groups (14 patients in each group). Secondary: Serious bleeding events affected 18 patients taking cilostazol and 22 patients taking placebo. The rates of bleeding events were similar in patients who used aspirin, aspirin plus clopidogrel or anticoagulants at any time during the course of the study.
Hiatt et al.[133] (2017) Ticagrelor 90 mg twice daily vs clopidogrel 75 mg once daily	DB, MC, RCT Patients ≥50 years of age with symptomatic PAD and one of two inclusion criteria: previous revascularization of the lower limbs for symptomatic disease more than 30 days before randomization or hemodynamic evidence of peripheral artery disease, as evidenced by an ankle–brachial index (ABI) of 0.80 or less at screening	N=13,885 Median follow-up of 30 months	Primary: First occurrence of any event in the composite of cardiovascular death, myocardial infarction, or ischemic stroke Secondary: Acute limb ischemia leading to hospitalization	Primary: The primary efficacy composite end point occurred in 751 of 6930 patients (10.8%) in the ticagrelor group and in 740 of 6955 (10.6%) in the clopidogrel group (HR, 1.02; 95% CI, 0.92 to 1.13; P=0.65). Secondary: The only significant between-group difference was in the rate of ischemic stroke, which occurred in 1.9% of the patients in the ticagrelor group, versus 2.4% in the clopidogrel group (HR, 0.78; 95% CI, 0.62 to 0.98; P=0.03). Other key secondary and composite end points including acute limb ischemia and revascularization were similar in the two groups.
Morrow et al.[134] (2012) TRA2P-TIMI 50 Vorapaxar 2.5 mg	DB, MC, RCT Patients with a history of atherosclerosis or	N=26,449 Median follow-up of 30 months	Primary: Composite of CV death, MI, or stroke	Primary: At three years, the primary end point had occurred in 1028 patients (9.3%) in the vorapaxar group, as compared with 1176 patients (10.5%) in the placebo group (HR, 0.87; 95% CI, 0.80 to 0.94; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs placebo Concomitant medical therapy, including the use of other antiplatelet agents, was managed by the clinicians according to local standards of care	PAD associated with a history of intermittent claudication in conjunction with either an ankle–brachial index of less than 0.85 or previous revascularization for limb ischemia	(patients with a history of stroke in the vorapaxar group discontinued therapy due to intracranial hemorrhage rates after a median of 24 months)	Secondary: Composite of CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization; GUSTO moderate or severe bleeding	Among patients with no history of stroke, the primary end point occurred in 8.3% of patients in the vorapaxar group, as compared with 9.6% of those in the placebo group (HR, 0.84; 95% CI, 0.76 to 0.93; P<0.001). Secondary: The major secondary end point of cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization occurred in 1259 patients (11.2%) in the vorapaxar group, as compared with 1417 patients (12.4%) in the placebo group (HR, 0.88; 95% CI, 0.82 to 0.95; P=0.001). The rate of death from any cause did not differ significantly between the vorapaxar group and the placebo group (5.0 and 5.3%, respectively; HR, 0.95; 95% CI, 0.85 to 1.07; P=0.41). The major safety end point of moderate or severe bleeding occurred in 438 patients (4.2%) in the vorapaxar group, as compared with 267 patients (2.5%) in the placebo group (HR, 1.66; 95% CI, 1.43 to 1.93; P<0.001). Among patients with a history of stroke, the rate of intracranial hemorrhage in the vorapaxar group was 2.4%, as compared with 0.9% in the placebo group (P<0.001). Among patients without a history of stroke, the rates of intracranial hemorrhage were lower in the two study groups (0.6% in the vorapaxar group and 0.4% in the placebo group; P=0.049).
Scirica et al.[135] (2012) TRA2P-TIMI 50 Vorapaxar 2.5 mg daily vs placebo Concomitant medical therapy, including the use of other antiplatelet agents, was managed by the	Subgroup analysis of TRA2P-TIMI 50 Patients enrolled in the TRA2P-TIMI 50 trial with a qualifying MI within the previous 2 weeks to 12 months	N=17,779 of 26,449 Median follow-up of 30 months (patients with a history of stroke in the vorapaxar group discontinued therapy due to intracranial	Primary: First, a composite of CV death, MI, or stroke, followed by CV death, MI, stroke, or urgent coronary revascularization, and then CV death or MI Secondary: GUSTO moderate or severe bleeding	Primary: The vorapaxar group had 610 patients (8.1%, 3-year Kaplan-Meier estimate) versus 750 patients in the placebo group (9.7%, 3-year Kaplan-Meier estimate) with CV death, MI, or stroke (HR, 0.80, 95% CI 0.72 to 0.89; P<0.0001). The incidence of the composite of CV death, MI, stroke, or urgent coronary revascularization was 10.5% in the vorapaxar group compared with 12.1% in the placebo group (HR, 0.83; 0.76 to 0.92; P=0.0001). Chance of CV death or MI was lower in patients allocated to vorapaxar than in those allocated to placebo (7.2 vs 8.6%, 3-year Kaplan-Meier estimate; P=0.0003). Secondary: The principal safety endpoint of GUSTO moderate or severe bleeding occurred in 241 of 8880 patients (3.4%, 3-year Kaplan-Meier estimate) in the vorapaxar group compared with 151 of 8849 patients (2.1%, 3-year Kaplan-Meier estimate) in the placebo group (HR, 1.61; 1.31 to 1.97;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clinicians according to local standards of care		hemorrhage rates after a median of 24 months)		P<0.0001). For all patients who qualified for the trial with myocardial infarction, risk of CV death, MI, stroke, urgent coronary revascularization, or GUSTO moderate or severe bleeding was lower in the vorapaxar group than in the placebo group (12.5 vs 13.4%; P=0.038).
Morrow et al.[136] (2013) TRA2P-TIMI 50 Vorapaxar 2.5 mg daily vs placebo Concomitant medical therapy, including the use of other antiplatelet agents, was managed by the clinicians according to local standards of care	Subgroup analysis of TRA2P-TIMI 50 Patients enrolled in the TRA2P-TIMI 50 trial with a prior ischemic stroke	N=4,883 (out of 26,449 total) Median follow-up of 24 months	Primary: First, a composite of CV death, MI, or stroke, followed by CV death, MI, stroke, or urgent coronary revascularization, and then CV death or MI Secondary: GUSTO moderate or severe bleeding	Primary: For patients who qualified with an ischemic stroke, the 3-year incidence of CV death, MI, or stroke was 13.0% in the vorapaxar group compared with 11.7% in the placebo group; hazard ratio (HR) 1.03 (95% CI, 0.85 to 1.25; P=0.75). No significant difference between vorapaxar and placebo was found in any of the efficacy end points examined. In particular, recurrent stroke alone was not reduced with vorapaxar (10.1 vs 7.5%; HR, 1.13; 95% CI, 0.90 to 1.40; P=0.30) in this cohort. Secondary: GUSTO moderate or severe bleeding was higher in patients treated with vorapaxar compared with placebo (4.2 vs 2.4%; HR, 1.93; 95% CI, 1.33 to 2.79; P<0.001). Intracranial hemorrhage, inclusive of intracerebral and subdural bleeding, was significantly increased with vorapaxar (2.5 vs 1.0%; HR, 2.52; 95% CI, 1.46 to 4.36; P<0.001).
Bonaca et al.[137] (2013) TRA2P-TIMI 50 Vorapaxar 2.5 mg daily vs placebo Concomitant medical	Subgroup analysis of TRA2P-TIMI 50 Patients enrolled in the TRA2P-TIMI 50 trial with PAD	N=3,787 (out of 26,449 total) Median follow-up of 36 months	Primary: First, a composite of CV death, MI, or stroke, followed by CV death, MI, stroke, or urgent coronary revascularization, and then CV death or MI; GUSTO moderate or severe bleeding	Primary: Vorapaxar did not significantly reduce the composite of CV death, MI, or stroke compared with placebo (11.3% vs 11.9%; HR, 0.94; 95% CI, 0.78 to 1.14; P=0.53) or CV death, MI, stroke, or urgent coronary revascularization (P=0.57). Compared with placebo, in the PAD cohort, vorapaxar increased the risk of bleeding, including GUSTO moderate or severe bleeding (7.4 vs 4.5%; HR, 1.62; 95% CI, 1.21 to 2.18; P=0.001) The rates of intracranial hemorrhages with vorapaxar compared with placebo were 0.9 vs 0.4% (HR, 2.03; 95% CI, 0.82 to 5.02; P=0.13)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy, including the use of other antiplatelet agents, was managed by the clinicians according to local standards of care			Secondary: Acute limb ischemia, peripheral revascularization (urgent and elective), and urgent hospitalization for vascular cause of an ischemic nature	Secondary: Vorapaxar significantly reduced the risk of limb ischemic events, including hospitalization for acute limb ischemia (2.3 vs 3.9%; HR, 0.58; 95% CI, 0.39 to 0.86; P=0.006) and peripheral revascularization (18.4 vs 22.2%; HR, 0.84; 95% CI, 0.73 to 0.97; P=0.017). This reduction was consistent for both urgent (3.1 vs 4.7%; HR, 0.65; 95% CI, 0.46 to 0.91; P=0.012) and elective (16.5 vs 19.5%; HR, 0.86; 95% CI, 0.74 to 0.9995; P=0.049) peripheral revascularization.

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice-daily, ER=extended-release, IR=immediate-release, QD=once-daily
Study abbreviations: AC=active-controlled, CS=cross sectional, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OB=observational, OL=open-label, PA=parallel arm, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=cross over trial
Miscellaneous abbreviations: ACS=acute coronary syndrome, BARC= Bleeding Academic Research Consortium, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, CT=computerized tomography, CV=cardiovascular, FEV_1=forced expiratory volume in one second, GFR=glomerular filtration rate, GP IIb/IIIa inhibitor=glycoprotein IIb/IIIa inhibitor, GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries, HR=hazard ratio, INR=International Normalized Ratio, IRR=incidence rate ratio, ITT=intention to treat, IU=international units, MES=microembolic signal, MI=myocardial infarction, MRI=magnetic resonance imaging, NSTE ACS=non-ST-segment elevation acute coronary syndromes, NSTEMI=non-ST-segment elevation myocardial infarction, OR=odds ratio, PAD=peripheral arterial disease, PCI=percutaneous coronary intervention, PPI=proton pump inhibitor, RR=relative risk, STEMI=ST-segment elevation myocardial infarction, TIA=transient ischemic attack, TIMI=thrombolysis in myocardial infarction, TRACER=Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome, TRA2P-TIMI 50=Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction

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 14. Relative Cost of the Platelet-Aggregation Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cilostazol	tablet	Pletal®*	$$$$	$
Clopidogrel	tablet	Plavix®*	$$$$	$
Prasugrel	tablet	Effient®*	$$$$$	$
Ticagrelor	tablet	Brilinta®	$$$$$	N/A
Vorapaxar	tablet	Zontivity®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The platelet-aggregation inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes (ACS), angina, intermittent claudication, myocardial infarction (MI), stroke, and transient ischemic attack (TIA). They are also approved for the prevention of thrombosis in patients undergoing cardiovascular procedures and/or surgery and reduction in death and hospitalization due to heart failure.[1-7] Cilostazol, clopidogrel, and prasugrel are available generically.

Aspirin has been the most frequently studied antiplatelet agent and is usually the reference drug to which other treatments are compared.[48] Aspirin is recommended as the first-line agent in most of the antiplatelet treatment guidelines for general use. Aspirin is recommended as a first-line option for the initial management of noncardioembolic stroke or TIA, ACS, and MI, as well as for primary and secondary prevention in patients with cerebrovascular, cardiovascular, and peripheral vascular diseases. Low-dose aspirin (75 to 150 mg/day) is an effective antiplatelet regimen for long-term use, but in acute settings, an initial loading dose of ≥150 mg may be required. Other platelet inhibitors are usually reserved for patients with contraindications or severe intolerance to aspirin or who have failed aspirin monotherapy or in high-risk patients when dual antiplatelet therapy is recommended. Dual antiplatelet therapy with aspirin plus clopidogrel, prasugrel, or ticagrelor is recommended for patients with ACS (non ST-segment elevation myocardial infarction [NSTEMI] and unstable angina). Antiplatelet therapy is also recommended in patients with ST-segment elevation myocardial infarction (STEMI). For patients with noncardioembolic ischemic strokes or TIAs, fixed-dose aspirin and dipyridamole is suggested instead of aspirin alone, and clopidogrel may be considered instead of aspirin alone to reduce the risk of recurrent stroke and other cardiovascular events.[13-22] For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination product has been studied in patients who have had an event while receiving aspirin.[16]

Clopidogrel is an adenosine diphosphate receptor antagonist and has been shown to significantly reduce the odds of a serious vascular event in high-risk patients. The CAPRIE trial reported that clopidogrel significantly reduced the combined risk of ischemic stroke, MI, and vascular death by 8.7% compared to aspirin in patients with a recent ischemic stroke, MI, or established peripheral vascular disease. In a subanalysis of over 6,000 patients who were enrolled in the trial based on a recent ischemic stroke, clopidogrel reduced the risk of the composite endpoint by 7.3% and stroke by 8.0% compared to aspirin; however, these differences were not statistically significant.[50] On the basis of the CURE, COMMIT, and CLARITY trials, clopidogrel received a Food and Drug Administration (FDA) indication for the reduction of atherothrombotic events in patients with ACS and MI, and clopidogrel has been incorporated into the current treatment guidelines for the management of these conditions.[17,19,53,54,117]

Prasugrel is an adenosine diphosphate receptor antagonist which has been reported to be the most potent of these agents and to have more desirable characteristics when compared to clopidogrel with regards to drug-drug interactions and interpatient enzyme variability.[8-10] Approval of this agent was based on the results from the TRITON-TIMI 38 trial, in which prasugrel was significantly more effective in reducing ischemic events in patients with ACS who underwent percutaneous coronary intervention (PCI) intervention. Of note, no reduction in the mortality rate was seen with prasugrel, and a significantly greater incidence of major, minor, life-threatening, and fatal bleeding events was associated with prasugrel.[106] The overall recommendation for patients with a STEMI in which PCI is planned is for a thienopyridine to be used, with both clopidogrel and prasugrel listed as potential options. Of note, use of prasugrel in STEMI patients with a prior history of stroke or TIA undergoing primary PCI is not recommended.[19]

Ticagrelor is indicated to reduce the rate of cardiovascular death, MI, and stroke in patients with ACS or a history of MI. The package insert states that "for at least the first 12 months following ACS, it is superior to clopidogrel." Ticagrelor has also been approved for reducing the rate of MI or stroke in patients with coronary artery disease (CAD) and the risk of stroke in patients with acute ischemic stroke or high-risk transient ischemic stroke (TIA). It is also approved to reduce the rate of stent thrombosis in patients who have been stented for treatment of ACS.[3] As a cyclopentyltriazolopyrimidine, ticagrelor works in a similar manner to the other thienopyridine platelet inhibitors (clopidogrel, prasugrel); however, ticagrelor is a reversible inhibitor of the $P2Y_{12}$ receptors. In addition, ticagrelor is not a prodrug and therefore does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.[2,3] The pivotal clinical trial

establishing the safety and efficacy of ticagrelor in reducing the rate of thrombotic cardiovascular events in patients with ACS is the PLATO trial. PLATO was a large, international, prospective, double-blind, randomized-controlled trial comparing ticagrelor and clopidogrel in hospitalized patients with documented ACS, with or without ST-segment elevation (N=18,624). After 12 months of treatment, ticagrelor significantly reduced the primary composite endpoint of cardiovascular death, MI, or stroke, without increasing the risk of major bleeding.[53] Within the United States, clopidogrel, prasugrel, and ticagrelor are all recommended as potential options in patients receiving PCI, while clopidogrel and ticagrelor are both recommended as potential options in patients with unstable angina/NSTEMI who are not undergoing PCI.[17,21] The 2015 European Society of Cardiology guidelines recommend that patients presenting without persistent ST-elevation receive dual antiplatelet therapy with aspirin and a platelet inhibitor. Specifically, ticagrelor is recommended for all patients at moderate to high risk of ischemic events, regardless of initial treatment strategy (i.e., invasive vs noninvasive), including those pretreated with clopidogrel. Prasugrel is recommended for $P2Y_{12}$ inhibitor-naïve patients who are proceeding to PCI, while clopidogrel is recommended for patients who cannot receive ticagrelor or prasugrel.[18]

Vorapaxar is indicated for the reduction of thrombotic cardiovascular events in patients with a history of MI or with peripheral arterial disease (PAD).[6] The TRACER study was a randomized, double-blind, placebo-controlled trial evaluating the efficacy of vorapaxar in addition to standard therapy in 12,944 patients who had acute coronary syndromes without ST-segment elevation. This trial was stopped early due to a significant increase in the risk of major bleeding, including intracranial hemorrhage, in vorapaxar-treated patients. The preliminary clinical outcomes data showed no significant advantage of vorapaxar over placebo in preventing the primary composite endpoint of death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization (P=0.07).[12] Vorapaxar increased the rate of moderate or severe bleeding, as compared with placebo (P<0.001).[12] FDA approval of vorapaxar was based on the TRA2P-TIMI 50 trial. A population of 26,449 patients with peripheral arterial disease or a history of MI or ischemic stroke was randomized to receive either vorapaxar or placebo, in addition to standard care. After two years, the data and safety monitoring board recommended that patients with a history of stroke stop taking vorapaxar because of an increased risk of intracranial hemorrhage; the trial was continued in all other patients. At three years, the composite efficacy endpoint of cardiovascular death, MI, or stroke had occurred in 9.3% of patients treated with vorapaxar, compared to 10.5% of those given placebo, a statistically significant difference.[135] In a prespecified subgroup analysis, among the 17,779 patients with a previous MI, the primary endpoint occurred in 8.1% of those taking vorapaxar compared to 9.7% of those taking placebo, a statistically significant difference.[136] In another subgroup analysis, among the 3,787 patients who had peripheral arterial disease, vorapaxar did not significantly reduce the composite endpoint of cardiovascular death, MI, or stroke compared with placebo, but it did significantly reduce the rate of hospitalization for acute limb ischemia (2.3 vs 3.9%).[137] Due to the increased risk of bleeding events with vorapaxar, it is contraindicated in patients with a history of stroke, transient ischemic attack, intracranial hemorrhage, or active pathologic bleeding.[6]

The effectiveness of clopidogrel is dependent on its activation to an active metabolite by cytochrome P450 (CYP) 2C19. Clopidogrel forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Consider alternative treatments in patients identified as CYP2C19 poor metabolizers.[5] Prasugrel can cause significant bleeding and should not be used in patients with active bleeding or a history of TIA or stroke. It is also not recommended in patients ≥75 years of age due to the increased risk of fatal and intracranial bleeding and because of uncertain benefit, except in high-risk situations.[4]

There is insufficient evidence to support that one brand platelet-aggregation inhibitor 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 platelet-aggregation inhibitors 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 platelet-aggregation 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Vasodilating Agents, Miscellaneous
AHFS Class 241292
February 7, 2024

I. Overview

The miscellaneous vasodilating agents play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes, myocardial infarction, stroke, and transient ischemic attack.[1-4]

The miscellaneous vasodilating agents exert their pharmacologic effects through several different mechanisms. Aspirin irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative, thromboxane A2, via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation. The mechanism of action of dipyridamole is not completely understood; however, it may involve its ability to increase the concentrations of adenosine, a platelet aggregation inhibitor and a coronary vasodilator, and cyclic adenosine monophosphate, which decreases platelet activation.[1-4]

Vericiguat is a stimulator of soluble guanylate cyclase (sGC). When the enzyme binds with nitric oxide it catalyzes the synthesis of intracellular cyclic guanosine monophosphate (cGMP) which regulates vascular tone, cardiac contractility, and cardiac modeling. Heart failure is associated with decreased activity of sGC which may contribute to myocardial and vascular dysfunction. Vericiguat increases levels of cGMP by stimulating sGC and causes smooth muscle relaxation and vasodilation.[3]

The vasodilating agents, miscellaneous has been separated from the platelet-aggregation inhibitors. Currently, dipyridamole and aspirin-dipyridamole are available generically. This review encompasses all dosage forms and strengths. This class was last reviewed in February 2022.

Table 1. Vasodilating Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dipyridamole	injection, tablet	N/A	dipyridamole
Vericiguat	tablet	Verquvo®	none
Combination Products			
Aspirin and dipyridamole	extended-release capsule	N/A	aspirin and dipyridamole

*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 treatment guidelines that incorporate the use of the vasodilating agents, miscellaneous are summarized in Table 2.

Table 2. Treatment Guidelines Using the Vasodilating Agents, Miscellaneous

Clinical Guideline	Recommendations
American College of Chest Physicians: **Antithrombotic Therapy and Prevention of Thrombosis, 9th edition (2012)**[5]	<u>Management of anticoagulant therapy</u> • For outpatients, vitamin K antagonist (VKA) therapy with warfarin 10 mg/day for the first two days, followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose is suggested. • Routine use of pharmacogenetic testing for guiding doses of VKA therapy is not recommended.

Clinical Guideline	Recommendations
	• For acute venous thromboembolism (VTE), it is suggested that VKA therapy be started on day one or two of low molecular weight heparin (LMWH) or low dose unfractionated heparin (UFH) therapy rather than waiting for several days to start. • For VKA therapy with stable INRs, INR testing frequency of up to 12 weeks is suggested rather than every four weeks. • For patients receiving previously stable VKA therapy who present with a single out-of-range INR ≤0.5 below or above therapeutic, it is suggested to continue the current dose and test the INR within one to two weeks. • For patients receiving stable VKA therapy presenting with a single subtherapeutic INR value, routine administering of bridging heparin is not recommended. • Routine use of vitamin K supplementation is suggested against with VKA therapy. • For patients receiving VKA therapy who are motivated and can demonstrate competency in self-management strategies, it is suggested that patient self-management be utilized rather than usual outpatient INR monitoring. • For maintenance VKA dosing, it is suggested that validated decision support tools be utilized rather than no decision support. • Concomitant use of nonsteroidal anti-inflammatory drugs and certain antibiotics should be avoided in patients receiving VKA therapy. • Concomitant use of platelet inhibitors should be avoided in patients receiving VKA therapy, except in situations where benefit is known or is highly likely to be greater than harm from bleeding. • With VKA therapy, a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended rather than a lower (<2.0) or higher (range, 3.0 to 5.0) range. • In patients with antiphospholipid syndrome with previous arterial or VTE, VKA therapy should be titrated to a moderate intensity INR (range, 2.0 to 3.0) rather than higher intensity (range, 3.0 to 4.5). • For discontinuations of VKA therapy, it is suggested that discontinuation be done abruptly rather than gradual tapering of the dose. • For initiation of intravenous (IV) UFH, the initial bolus and rate of continuous infusion should be weight adjusted or fixed-dose rather than alternative regimens. • In outpatients with VTE receiving subcutaneous (SC) UFH, dosing should be weight-based without monitoring rather than fixed or weight-adjusted dosing with monitoring. • A reduction in therapeutic LMWH dose is suggested in patients with severe renal insufficiency rather than using standard doses. • In patients with VTE and body weight >100 kg, the treatment dose of fondaparinux should be increased from 7.5 to 10 mg/day SC. • For INRs between 4.5 and 10.0 with VKA therapy and no evidence of bleeding, routine use of vitamin K is not recommended. • For INRs >10.0 with VKA therapy and no evidence of bleeding, it is suggested that oral vitamin K be administered. • In patients initiating VKA therapy, routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy is not recommended. • For VKA-associated major bleeding, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate is suggested over plasma. Additional use of vitamin K 5 to 10 mg administered by slow IV injection is recommended rather than reversal with coagulation factors alone. <u>Prevention of VTE in nonsurgical patients</u> • Acutely ill hospitalized medical patients at increased risk of thrombosis: anticoagulant thromboprophylaxis with LMWH, low dose UFH (two or three

Clinical Guideline	Recommendations
	times daily), or fondaparinux is recommended. Choice should be based on patient preference, compliance, and ease of administration, as well as on local factors affecting acquisition costs. • Acutely ill hospitalized patients at low risk of thrombosis: pharmacologic or mechanical prophylaxis is not recommended. • Acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding: anticoagulant thromboprophylaxis is not recommended. • Acutely ill hospitalized medical patients at increased risk for thrombosis who are bleeding or at high risk of major bleeding: optimal use of mechanical thromboprophylaxis is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, it is suggested that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis. • Acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis: extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay is suggested against. • Critically ill patients: routine ultrasound screening for deep vein thrombosis (DVT) is suggested against. • Critically ill patients: use of LMWH or low dose UFH thromboprophylaxis is suggested over no prophylaxis. • Critically ill patients who are bleeding or are at high risk for major bleeding: use of mechanical thromboprophylaxis until the bleeding risk decreases is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, pharmacologic thromboprophylaxis is suggested to be substituted for mechanical thromboprophylaxis. • Outpatients with cancer who have no additional risk factors for VTE: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is not recommended. • Outpatients with solid tumors who have additional risk factors for VTE with low risk of bleeding: prophylaxis with LMWH or low dose UFH is suggested over no prophylaxis. • Outpatients with cancer and indwelling central venous catheters: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is suggested against. • Chronically immobilized patients residing at home or at a nursing home: routine thromboprophylaxis is suggested against. • Long distance travelers at increased risk of VTE: frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible is suggested. • Long distance travelers at increased risk of VTE: use of properly fitted, below-knee graduated compression stockings during travel is suggested. For all other long distance travelers, use of graduated compression stockings is suggested against. • Long distance travelers: use of aspirin or anticoagulants to prevent VTE is suggested against. • Patients with asymptomatic thrombophilia: long term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE is not recommended. <u>Prevention of VTE in nonorthopedic surgical patients</u> • General and abdominal-pelvic surgery patients at very low risk for VTE: no specific pharmacologic or mechanical prophylaxis is recommended for use other than early ambulation. • General and abdominal-pelvic surgery patients at low risk for VTE: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are not at high risk major bleeding complications: LMWH, low dose UFH, or

Clinical Guideline	Recommendations
	mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at high risk for VTE who are not at high risk for major bleeding complications: LMWH or low dose UFH is recommended over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • High-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications: extended duration (four weeks) of LMWH prophylaxis is recommended over limited duration prophylaxis. • High-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • General and abdominal-pelvic surgery patients at high risk for VTE in whom both LMWH and UFH are contraindicated or unavailable and who are not at high risk for major bleeding complications: low dose aspirin, fondaparinux, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients: it is suggested that an inferior vena cava filter not be used for primary VTE prevention. • General and abdominal-pelvic surgery patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. • Cardiac surgery patients with an uncomplicated postoperative course: mechanical prophylaxis is suggested over either no prophylaxis or pharmacologic prophylaxis. • Cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications: adding pharmacologic prophylaxis with low dose UFH or LMWH to mechanical prophylaxis is suggested. • Thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding: low dose UFH or LWMH is suggested over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • Thoracic surgery patients who are at high risk for major bleeding: mechanical prophylaxis over no prophylaxis is suggested until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • Craniotomy patients: mechanical prophylaxis is suggested over no prophylaxis or pharmacologic prophylaxis. • Craniotomy patients at very high risk for VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Patients undergoing spinal surgery: mechanical prophylaxis is suggested over no prophylaxis, UFH, or LMWH. • Patients undergoing spinal surgery at high risk of VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Major trauma patients: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Major trauma patients at high risk for VTE: it is suggested that mechanical

Clinical Guideline	Recommendations
	prophylaxis be added to pharmacologic prophylaxis when not contraindicated by lower extremity injury. • Major trauma patients in whom LMWH and low dose UFH are contraindicated: mechanical prophylaxis is suggested over no prophylaxis when not contraindicated by lower extremity injury. It is suggested that either LMWH or low dose UFH be added when the risk of bleeding diminishes or the contraindication to heparin resolves. • Major trauma patients: it is suggested that an interior vena cava filter not be used for primary VTE prevention. • Major trauma patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. <u>Prevention of VTE in orthopedic surgery patients</u> • Total hip arthroplasty or total knee arthroplasty: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, aspirin, or an intermittent pneumatic compression device. • Hip fracture surgery: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, low dose UFH, adjusted-dose VKA, aspirin, or intermittent pneumatic compression device. • Patients undergoing major orthopedic surgery (total hip arthroplasty, total knee arthroplasty, hip fracture surgery) and receiving LMWH as thromboprophylaxis: it is recommended to start either 12 hours or more preoperatively or postoperatively rather than within four hours or less preoperatively or postoperatively. • Total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, or aspirin. • Hip replacement surgery, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, low dose UFH, adjusted-dose VKA, or aspirin. • Major orthopedic surgery: it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days. • Major orthopedic surgery: it is suggested to use dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the hospital stay. • Major orthopedic surgery in patients at an increased risk of bleeding: intermittent pneumatic compression device or no prophylaxis is suggested over pharmacologic prophylaxis. • Major orthopedic surgery in patients who decline or are uncooperative with injections or intermittent pneumatic compression device: apixaban or dabigatran etexilate mesylate (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran etexilate mesylate are unavailable) is recommended over alternative forms of prophylaxis. • Major orthopedic surgery in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical prophylaxis: inferior vena cava filter placement for primary prevention of VTE is suggested against over no thromboprophylaxis. • Asymptomatic patients following major orthopedic surgery: Doppler

Clinical Guideline	Recommendations
	ultrasound screening before hospital discharge is not recommended. • Patients with lower leg injuries requiring leg immobilization: no prophylaxis is suggested rather than pharmacologic thromboprophylaxis. • Knee arthroscopy in patients without a history of prior VTE: no thromboprophylaxis is suggested rather than prophylaxis. <u>Antithrombotic therapy for VTE disease</u> • Acute DVT of the leg or pulmonary embolism (PE) treated with VKA therapy: initial treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) is recommended over no such initial treatment. • High clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment while awaiting the results of diagnostic tests. • Intermediate clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment if the results of diagnostic tests are expected to be delayed for more than four hours. • Low clinical suspicion of acute VTE or PE: it is suggested to not treat with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours. • Acute isolated distal DVT of the leg without severe symptoms or risk factors for extension: serial imaging of the deep veins for two weeks is suggested over initial anticoagulation. • Acute isolated distal DVT of the leg and severe symptoms or risk factors for extension: initial anticoagulation is suggested over serial imaging of the deep veins. • Acute isolated distal DVT of the leg in patients managed with initial anticoagulation: using the same approach as for patients with acute proximal DVT is recommended. • Acute isolated distal DVT of the leg who are managed with serial imaging: no anticoagulation if the thrombus does not extend is recommended; anticoagulation is suggested if the thrombus extends but remains confined to the distal veins; and anticoagulation is recommended if the thrombus extends into the proximal veins. • Acute DVT of the leg or PE: early initiation of VKA therapy is recommended over delayed initiation, and continuation of parenteral anticoagulation for a minimum on five days and until the INR is 2.0 or above for at least 24 hours. • Acute DVT of the leg or PE: LMWH or fondaparinux is suggested over IV or SC UFH. • Patients with acute DVT of the leg or PE receiving LMWH: once daily LMWH administration is suggested over twice daily administration. • Acute DVT of the leg and home circumstances are adequate: initial treatment at home is recommended over treatment in hospital. • Low risk PE and home circumstances are adequate: early discharge is suggested over standard discharge. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over catheter-directed thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over systemic thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over venous thrombectomy. • Acute DVT of the leg in patients who undergo thrombosis removal: the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal is recommended. • Acute DVT of the leg: use of an inferior vena cava filter in addition to anticoagulants is not recommended.

Clinical Guideline	Recommendations
	• Acute proximal DVT of the leg in patients with contraindication to anticoagulation: use of an inferior vena cava filter is recommended. • Acute proximal DVT of the leg in patients with an inferior vena cava filter inserted as an alternative to anticoagulation: a conventional course of anticoagulant therapy is suggested if the risk of bleeding resolves. • Acute DVT of the leg: early ambulation is suggested over initial bed rest. • Acute VTE in patients receiving anticoagulant therapy: long term therapy is recommended over stopping anticoagulant therapy after about one week of initial therapy. • Acute symptomatic DVT of the leg: compression stockings are suggested. • Acute PE associated with hypotension in patients who do not have a high bleeding risk: systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension: systemically administered thrombolytic therapy is not recommended. • In selected patients with acute PE not associated with hypotension and with a low bleeding risk who initial clinical presentation or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension: administration of thrombolytic therapy is suggested. • Proximal DVT of the leg or PE provoked by surgery: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment of a longer time limited period, or extended therapy. • Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment for a longer time limited period, extended therapy if there is high bleeding risk. Anticoagulation treatment for three months is suggested over extended therapy if there is a low or moderate bleeding risk. • Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor: treatment with anticoagulation for three months is suggested over treatment for a shorter period, and anticoagulation treatment for three months is recommended over treatment of longer time limited period or extended therapy. • Unprovoked DVT of the leg or PE: treatment with anticoagulation for three months is recommended over treatment of a shorter duration. After three months, patients should be evaluated for the risk-benefit ratio of extended therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a low or moderate bleeding risk: extended anticoagulant therapy is suggested over three months of therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a high bleeding risk: three months of anticoagulant therapy is recommended over extended therapy. • First VTE that is an unprovoked isolated distal DVT of the leg: three months of anticoagulation therapy is suggested over extended therapy in those with a low or moderate bleeding risk, and three months of anticoagulant treatment is recommended in those with a high bleeding risk. • Second unprovoked VTE or PE: extended anticoagulant therapy is recommended over three months of therapy in those who have a low bleeding risk, and extended anticoagulant therapy is suggested in patients with a moderate bleeding risk. • Second unprovoked VTE or PE in patients with a high bleeding risk: three months of anticoagulant therapy is suggested over extended therapy. • DVT of the leg or PE and active cancer: if the risk of bleeding is not high, extended anticoagulation therapy is recommended over three months of

Clinical Guideline	Recommendations
	therapy, and if there is a high bleeding risk, extended anticoagulant therapy is suggested. • DVT of the leg or PE in patients treated with VKA: a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended over a lower (<2.0) or higher (range, 3.0 to 5.0) range for all treatment durations. • DVT of the leg or PE in patients with no cancer: VKA therapy is suggested over LMWH for long-term therapy. For patients with DVT or PE and no cancer who are not treated with VKA therapy, LMWH is suggested over dabigatran etexilate mesylate or rivaroxaban for long term therapy. • DVT of the leg or PE and cancer: LMWH is suggested over VKA therapy. In patients with DVT of the leg or PE and cancer who are not treated with LMWH, VKA is suggested over dabigatran etexilate mesylate or rivaroxaban for long-term therapy. • DVT of the leg or PE in patients who receive extended therapy: treatment with the same anticoagulant chosen for the first three months is suggested. • Patients incidentally found to have asymptomatic DVT of the leg or PE: treatment with the same anticoagulant is suggested as for comparable patients with symptomatic DVT or PE. • In patients with chronic thromboembolic pulmonary hypertension, extended anticoagulation is recommended over stopping therapy. • Superficial vein thrombosis of the lower limb of at least 5 cm in length: use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation. • Superficial vein thrombosis in patients treated with anticoagulation: fondaparinux 2.5 mg/day is suggested over a prophylactic dose of LMWH. • Upper-extremity DVT that involves the axillary or more proximal veins: acute treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) over no such acute treatment. • Acute upper-extremity DVT that involves the axillary or more proximal veins: LMWH or fondaparinux is suggested over IV or SC UFH, and anticoagulation therapy alone is suggested over thrombolysis. • Upper-extremity DVT in patients undergoing thrombolysis: the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis is recommended. • In most patients with upper-extremity DVT that is associated with a central venous catheter: it is suggested that the catheter not be removed if it is functional and there is an ongoing need for the catheter. • Upper-extremity DVT that involves the axillary or more proximal veins: a minimum duration of anticoagulation of three months is suggested over a shorter duration. • Upper-extremity DVT that is associated with a central venous catheter that is removed: three months of anticoagulation is recommended over a longer duration of therapy in patients with no cancer, and this is suggested in patients with cancer. • Upper-extremity DVT that is associated with a central venous catheter that is not removed: it is recommended that anticoagulation is continued as long as the central venous catheter remains over stopping after three months of treatment in patients with cancer, and this is suggested in patients with no cancer. • Upper-extremity DVT that is not associated with a central venous catheter or with cancer: three months of anticoagulation is recommended over a longer duration of therapy. • Acute symptomatic upper-extremity DVT: use of compression sleeves or venoactive medications is suggested against. • Symptomatic splanchnic vein thrombosis: anticoagulation is recommended

Clinical Guideline	Recommendations
	over no anticoagulation. • Symptomatic hepatic vein thrombosis: anticoagulation is suggested over no anticoagulation. • In patients with incidentally detected splanchnic vein thrombosis or hepatic vein thrombosis: no anticoagulation is suggested over anticoagulation. <u>Antithrombotic therapy for atrial fibrillation (AF)</u> • Patients with AF, including those with paroxysmal AF, who are at low risk of stroke: no therapy is suggested over antithrombotic therapy. For patients who choose antithrombotic therapy, aspirin is suggested over oral anticoagulation or combination therapy with aspirin and clopidogrel. • Patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke: oral anticoagulation is recommended over no therapy. Oral anticoagulation is suggested over aspirin or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel are suggested over aspirin. • Patients with AF, including those with paroxysmal AF, who are at high risk of stroke: oral anticoagulation is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel is recommended over aspirin. • Patients with AF, including those with paroxysmal AF: for recommendations in favor of oral anticoagulation, dabigatran etexilate mesylate 150 mg twice daily is suggested over adjusted-dose VKA therapy (target INR range, 2.0 to 3.0). • Patients with AF and mitral stenosis: adjusted-dose VKA therapy is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take adjusted-dose VKA therapy, combination therapy with aspirin and clopidogrel is recommended over aspirin alone. • Patients with AF and stable coronary artery disease and who choose oral anticoagulation: adjusted-dose VKA therapy alone is suggested over the combination of adjusted-dose VKA therapy and aspirin. • Patients with AF at high risk of stroke during the first month after placement of a bare-metal stent or the first three to six months after placement of a drug-eluting stent: triple therapy (e.g., VKA therapy, aspirin, and clopidogrel) is suggested over dual antiplatelet therapy (e.g., aspirin and clopidogrel). After this initial period, a VKA plus a single antiplatelet agent is suggested over a VKA alone. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate risk of stroke during the first 12 months after placement of a stent: dual antiplatelet therapy is suggested over triple therapy. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate to high risk of stroke who experience an acute coronary syndrome (ACS) and do not undergo stent placement, for the first 12 months: adjusted-dose VKA therapy plus single antiplatelet therapy is suggested over dual antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at low risk of stroke: dual antiplatelet therapy is suggested over adjusted-dose VKA therapy plus single antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.

Clinical Guideline	Recommendations
	• Patients with AF being managed with a rhythm control strategy: it is suggested that antithrombotic therapy decisions follow the general risk-based recommendations for patients with nonrheumatic AF, regardless of the apparent persistence of normal sinus rhythm. • Patients with atrial flutter: it is suggested that antithrombotic therapy decisions follow the same risk-based recommendations as for AF. <u>Antithrombotic therapy for ischemic stroke</u> • In patients with acute ischemic stroke or transient ischemic attack (TIA), early (within 48 hours) aspirin 160 to 325 mg is recommended over therapeutic parenteral anticoagulation. • In patients with a history of noncardioembolic ischemic stroke or TIA, aspirin (75 to 100 mg daily), clopidogrel (75 mg daily), aspirin-dipyridamole extended-release (ER) (25 mg-200 mg twice daily) or cilostazol (100 mg twice daily) is recommended over oral anticoagulants, the combination of clopidogrel plus aspirin or triflusal. o Clopidogrel or aspirin-dipyridamole ER is recommended over aspirin or cilostazol. • In patients with a history of ischemic stroke or TIA and AF, oral anticoagulation with dabigatran 150 mg twice daily is recommended over VKA therapy. o In patients who are unable to or choose not to take an oral anticoagulant, the combination of aspirin plus clopidogrel is recommended over aspirin alone. <u>Primary and secondary prevention of cardiovascular disease</u> • Patients ≥50 years of age without symptomatic cardiovascular disease: low dose aspirin (75 to 100 mg/day) is suggested over no aspirin therapy. • Patients with established coronary artery disease: long term single antiplatelet therapy with aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended over no antiplatelet therapy, and single antiplatelet therapy is suggested over dual antiplatelet therapy. • Patients in the first year after ACS who have not undergone percutaneous coronary intervention (PCI): dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day or clopidogrel 75 mg/day plus low dose aspirin 75 to 100 mg/day) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients in the first year after an ACS who have undergone PCI with stent placement: dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day, clopidogrel 75 mg/day plus low dose aspirin, or prasugrel 10 mg/day plus low dose aspirin) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients with anterior myocardial infarction (MI) and left ventricular thrombus, or at high risk for left ventricular thrombus, who do not undergo stenting: warfarin plus low dose aspirin (75 to 100 mg/day) is recommended over single antiplatelet therapy or dual antiplatelet therapy for the first three months. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, single antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who undergo bare-metal stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for one month is suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the

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	second and third month post-bare-metal stent is suggested over alternative regimens and alternative time frames for warfarin use. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus who undergo drug-eluting stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for up to three to six months is suggested over alternative regimens and alternative durations of warfarin therapy. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective PCI with placement of bare-metal stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for one month is recommended over single antiplatelet therapy. For the subsequent 11 months, dual antiplatelet therapy with combination low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. • Patients who have undergone elective PCI with placement of drug-eluting stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for three to six months is recommended over single antiplatelet therapy. After three to six months, continuation of dual antiplatelet therapy with low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested to be continued until 12 months over antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective bare-metal stent or drug-eluting stent placement: low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is recommended over cilostazol in addition to these drugs. Aspirin 75 to 100 mg/day or clopidogrel 75 mg/day as part of dual antiplatelet therapy is suggested over the use of either drug with cilostazol. Cilostazol 100 mg twice daily as a substitute for either low dose aspirin or clopidogrel as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class is suggested. • Patients with coronary artery disease undergoing elective PCI but no stent placement: for the first month dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients with systolic left ventricular dysfunction without established coronary artery disease and no left ventricular thrombus: it is suggested that antiplatelet therapy and warfarin not be used. • Patients with systolic left ventricular dysfunction without established coronary artery disease with identified acute left thrombus: moderate intensity warfarin for at least three months is suggested. • Patients with systolic left ventricular dysfunction and established coronary artery disease: recommendations are as per the established coronary artery disease recommendations. <u>Antithrombotic therapy in peripheral artery disease (PAD)</u> • In patients with asymptomatic PAD, aspirin 75 to 100 mg daily is recommended.

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	• In patients with symptomatic PAD, long-term therapy with aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) is recommended for secondary prevention of cardiovascular events. Dual antiplatelet therapy or the combination of an antiplatelet agent with moderate-intensity warfarin is not recommended.
	• Use of cilostazol in addition to aspirin or clopidogrel is recommended in patients with intermittent claudication refractory to exercise therapy and smoking cessation.
	• Use of prostanoids in addition to aspirin or clopidogrel is recommended in patients with symptomatic PAD and critical leg ischemia who are not candidates for vascular intervention.
	• In patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, long-term therapy with aspirin or clopidogrel is recommended over dual antiplatelet therapy.
	• Following peripheral artery bypass graft surgery, long-term therapy with aspirin or clopidogrel is recommended over the combination of antiplatelet agent plus warfarin. Clopidogrel plus aspirin for one year is recommended in patients undergoing below-knee bypass graft surgery with prosthetic grafts.
	• In patients with asymptomatic carotid stenosis, aspirin 75 to 100 mg daily is recommended.
	• In patients with symptomatic carotid stenosis, long-term therapy with clopidogrel (75 mg daily) or aspirin/dipyridamole ER (25 mg/200 mg twice daily) is recommended over aspirin (75 to 100 mg daily).
	
	<u>Antithrombotic and thrombolytic therapy for valvular disease</u>
	• Antithrombotic therapy in the first three months after surgery:
	  o In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, aspirin (50 to 100 mg/day) over VKA therapy is suggested in the first three months.
	  o In patients with transcatheter aortic bioprosthetic valves, aspirin (50 to 100 mg/day) plus clopidogrel (75 mg/day) is suggested over VKA therapy and over no antiplatelet therapy in the first three months.
	  o In patients with a bioprosthetic valve in the mitral position, VKA therapy over no VKA therapy for the first three months after valve insertion is suggested.
	• Long-term antithrombotic therapy for patients with bioprosthetic valves:
	  o In patients with bioprosthetic valves in normal sinus rhythm, aspirin therapy over no aspirin therapy after three months postoperative is suggested.
	• Early postoperative bridging to intermediate/long-term therapy (postoperative day 0 to 5):
	  o In patients with mechanical heart valves, bridging with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) over intravenous (IV) therapeutic UFH until stable on VKA therapy.
	• Long-term antithrombotic therapy for patients with mechanical valves:
	  o VKA therapy is recommended over no VKA therapy for long-term management.
	• Intensity of VKA therapy for patients with mechanical aortic valve prostheses:
	  o VKA therapy at a target of 2.5 over lower targets is suggested. A target of 2.5 is recommended over higher targets.
	• Intensity of VKA therapy for patients with mechanical mitral valve prostheses:
	  o VKA therapy with a target of 3.0 over lower INR targets is suggested.
	• Intensity of VKA therapy in patients with double mechanical valve or with additional risk factors:
	  o VKA therapy with a target of 3.0 is suggested over target INR 2.5.

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	• Antiplatelet agent in addition to VKA therapy for patients with mechanical aortic or mitral valve prostheses: o Patients who are at low risk of bleeding, adding over not adding an antiplatelet agent such as low-dose (50 to 100 mg/day) to VKA therapy is suggested. • For patients with mechanical aortic or mitral valves VKA therapy over antiplatelet agents is recommended. • In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, the use of antiplatelet therapy for the first three months is suggested over VKA therapy. • In patients undergoing aortic valve repair, aspirin (50 to 100 mg/day) is suggested over VKA therapy.
American College of Chest Physicians: **Antithrombotic Therapy for VTE Disease (2021)[6]**	<u>Choice of long-term (first three months) and extended (no scheduled stop date) anticoagulant</u> • In patients with proximal deep vein thrombosis (DVT) or pulmonary embolism (PE), long-term (three months) anticoagulant therapy is recommended over no such therapy. • In patients with DVT of the leg or PE and no cancer, as long-term (first three months) anticoagulant therapy, dabigatran, rivaroxaban, apixaban, or edoxaban is recommended over vitamin K antagonist (VKA) therapy. • No non-vitamin K oral anticoagulant is preferred over another. • Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. • In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term anticoagulant therapy, LMWH is recommended over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban. • In patients with DVT of the leg or PE who receive extended therapy, there is no need to change the choice of anticoagulant after the first three months. <u>Duration of anticoagulant therapy</u> • In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension, suggest serial imaging of the deep veins for two weeks over anticoagulation or (ii) with severe symptoms or risk factors for extension. suggest anticoagulation over serial imaging of the deep veins. • In patients with acute isolated distal DVT of the leg who are managed with serial imaging, (i) recommend no anticoagulation if the thrombus does not extend , (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins, and (iii) recommend anticoagulation if the thrombus extends into the proximal veins. • In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE, suggest clinical surveillance over anticoagulation or (ii) high risk for recurrent VTE, suggest anticoagulation over clinical surveillance. • In patients who are incidentally found to have asymptomatic PE, suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE. • In patients with cerebral vein/venous sinus thrombosis, recommend anticoagulation therapy for at least the treatment phase (first three months) over no anticoagulant therapy. • In patients with acute DVT of the leg, suggest anticoagulant therapy alone over interventional (thrombolytic, mechanical, or pharmaco-mechanical) therapy. • In patients with acute PE associated with hypotension (e.g., systolic BP <90 mmHg) who do not have a high bleeding risk, suggest systemically

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	administered thrombolytic therapy over no such therapy. • In most patients with acute PE not associated with hypotension, recommend against systemically administered thrombolytic therapy. • In patients with a proximal DVT of the leg or PE provoked by surgery, treatment with anticoagulation for three months is recommended over (i) treatment of a shorter period, (ii) treatment of a longer time-limited period (e.g., six, 12, or 24 months), or (iii) extended therapy (no scheduled stop date). • In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, treatment with anticoagulation for three months is recommended over (i) treatment of a shorter period and (ii) treatment of a longer time-limited period (e.g., six, 12, or 24 months). Treatment with anticoagulation for three months is suggested over extended therapy if there is a low or moderate bleeding risk, and treatment for three months is recommended over extended therapy if there is a high risk of bleeding. • In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, treatment with anticoagulation for three months is suggested over treatment of a shorter period, treatment with anticoagulation for three months is recommended over treatment of a longer time-limited period (e.g., six, 12, or 24 months), and treatment with anticoagulation for three months is recommended over extended therapy (no scheduled stop date). • In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, treatment with anticoagulation for at least three months is recommended over treatment of a shorter duration), and treatment with anticoagulation for three months is recommended over treatment of a longer time-limited period (e.g., six, 12, or 24 months). • In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk, extended anticoagulant therapy (no scheduled stop date) is suggested over three months of therapy, and (ii) high bleeding risk, three months of anticoagulant therapy is recommended over extended therapy (no scheduled stop date). • In patients with a second unprovoked VTE and who have a (i) low bleeding risk, extended anticoagulant therapy (no scheduled stop date) is recommended over three months; (ii) moderate bleeding risk, extended anticoagulant therapy is suggested over three months of therapy; or (iii) high bleeding risk, three months of anticoagulant therapy is suggested over extended therapy (no scheduled stop date). • In patients with "cancer-associated thrombosis" and who (i) do not have a high bleeding risk, extended anticoagulant therapy (no scheduled stop date) is recommended over three months of therapy, or (ii) have a high bleeding risk, extended anticoagulant therapy (no scheduled stop date) is suggested over three months of therapy. <u>Aspirin for extended treatment of VTE</u> • In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin is suggested over no aspirin to prevent recurrent VTE. <u>Whether to anticoagulate subsegmental PE</u> • In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE, clinical surveillance is suggested over anticoagulation or (ii) high risk for recurrent VTE, anticoagulation is suggested over clinical surveillance. <u>Treatment of acute PE out of the hospital</u>

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	• In patients with low-risk PE and whose home circumstances are adequate, treatment at home or early discharge is suggested over standard discharge (e.g., after the first five days of treatment). Systemic thrombolytic therapy for PE • In patients with acute PE associated with hypotension (e.g., systolic BP <90 mm Hg) who do not have a high bleeding risk, systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension, systemically administered thrombolytic therapy is NOT recommended. • In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, systemically administered thrombolytic therapy is suggested over no such therapy. Thrombolytic therapy in patients with upper extremity DVT • In patients with acute upper extremity DVT (UEDVT) that involves the axillary or more proximal veins, anticoagulant therapy alone is suggested over thrombolysis. • In patients with UEDVT who undergo thrombolysis, the same intensity and duration of anticoagulant therapy as in patients with UEDVT who do not undergo thrombolysis is recommended. Management of recurrent VTE on anticoagulant therapy • In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), switching to treatment with LMWH at least temporarily is suggested. • In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), increasing the dose of LMWH by about one-quarter to one-third is suggested. • Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy. A temporary switch to LMWH will usually be for at least one month.
American College of Cardiology/American Heart Association: **Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease (2016)**[7]	Recommendations for Antiplatelet Agents: • Antiplatelet therapy with aspirin alone (range 75 to 325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce myocardial infarction (MI), stroke, and vascular death in patients with symptomatic peripheral artery disease (PAD). • In asymptomatic patients with PAD (Ankle Brachial Index (ABI) ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death. • In asymptomatic patients with borderline ABI (0.91 to 0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain. • The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established. • DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization. • The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.

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	Recommendations for Statin Agents: • Treatment with a statin medication is indicated for all patients with PAD. Recommendations for Antihypertensive Agents: • Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. • The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD. Recommendations for Smoking Cessation: • Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit. • Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program. • Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places. Recommendations for Glycemic Control: • Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team. • Glycemic control can be beneficial for patients with critical limb ischemia (CLI) to reduce limb-related outcomes. Recommendations for Oral Anticoagulation: • The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain. • Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD. Recommendations for Cilostazol: • Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication. Recommendations for Pentoxifylline: Pentoxifylline is not effective for treatment of claudication.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2021)**[8]	Recommendations for Nonvalvular Atrial Fibrillation: • For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (~30 days) for AF is reasonable within six months of the index event. • VKA therapy, apixaban, dabigatran and rivaroxaban are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. ○ Selection of agent should be individualized based on risk factors, cost, tolerability, patient preference, drug interactions and other characteristics including renal function and time in INR therapeutic range if the patient has been taking VKA therapy. • Target INR for patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent or permanent AF on VKA therapy is 2.5 (range 2.0 to 3.0). • Combination oral anticoagulation (warfarin or a newer agent) with antiplatelet

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	therapy is not recommended for all patients after ischemic stroke or TIA. o Combination therapy is reasonable in patients with clinically apparent coronary artery disease particularly an acute coronary syndrome or stent placement. • For patients with ischemic stroke or TIA and AF who unable to take oral anticoagulants, aspirin alone is recommended. o Adding clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable. • For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms. • In the presence of high risk for hemorrhagic conversion, it is reasonable to delay initiation of oral anticoagulation beyond 14 days. • For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent) is reasonable, depending on perceived risk for thromboembolism and bleeding. • The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain. <u>Recommendations for Acute MI and LV Thrombus:</u> • Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months is recommended in most patients with ischemic stroke or TIA in this setting. o Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the American College of Chest Physicians. • Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging. • In patients with stroke or TIA and new LV thrombus (<3 months), the safety of anticoagulation with a direct oral anticoagulant to reduce risk of recurrent stroke is uncertain. • In patients with stroke or TIA in the setting of acute anterior MI with reduced ejection fraction <50% but not evidence of LV thrombus, empirical anticoagulation for at least three months might be considered to reduce the risk of recurrent cardioembolic stroke <u>Recommendations for Cardiomyopathy:</u> • In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus, anticoagulant therapy with a VKA is recommended for ≥3 months. • In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) and aspirin is reasonable in the absence of major contraindications. • In patients with ischemic stroke or TIA in the setting of LV noncompaction, treatment with VKA therapy can be beneficial to reduce the risk of recurrent stroke. In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized. • In patients with stroke or TIA and LVADs, treatment with dabigatran instead

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	of warfarin for the primary or secondary prevention of ischemic stroke or TIA causes harm. <u>Recommendations for Mitral Stenosis, Mitral Regurgitation, Mitral Prolapse, Mitral Annular Calcification, and Aortic Valve Disease</u>: • In patients with VHD (except moderate to severe mitral stenosis or a mechanical heart valve), ischemic stroke or TIA, and AF, DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin therapy. • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with INR target of 2.5 (range, 2.0 to 3.0) is recommended. • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (e.g., carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered instead of antiplatelet therapy. • For patients with rheumatic mitral valve disease who are prescribed VKA therapy after an ischemic stroke or TIA, antiplatelet therapy should not be routinely added. • For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered. • For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended. • For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification. • For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse. <u>Recommendations for Prosthetic Heart Valves:</u> • For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0 to 3.0). • For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5 to 3.5). • For patients with a mechanical aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/day to VKA therapy is recommended. • For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/day or increasing the target INR, depending on bleeding risk. • For patients with a bioprosthetic aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and no other indication for anticoagulation therapy beyond three to six months form the valve placement, long-term therapy with aspirin 75 to 100 mg/day is recommended in preference to long-term anticoagulation. • For patients with a bioprosthetic aortic or mitral valve who have a TIA, ischemic stroke, or systemic embolism despite antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered.

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	Recommendations for Noncardioembolic Stroke or TIA: • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. • Aspirin (50 to 325 mg/day) monotherapy, clopidogrel 75 mg daily, or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. • Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole. This recommendation also applies to patients who are allergic to aspirin. • For patients with recent minor noncardioembolic ischemic stroke or high-risk TIA, DAPT (aspirin plus clopidogrel) should be initiated within 12 to 24 hours of symptom onset and at least within seven days of onset. Therapy should be continued for 21 to 90 days, followed by single agent platelet therapy to reduce the risk of recurrent stroke. • For patients with recent minor to moderate stroke, high-risk TIA< or symptomatic intracranial or extracranial ≥30% stenosis of an artery, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events. • The selection of an antiplatelet agent should be individualized on the basis of patient risk facto profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics. • The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for two to three years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA). • For patients who have an ischemic stroke or TIA while taking aspirin, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established. • For patients with a history of ischemic stroke or TIA, AF and coronary artery disease, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet or VKA therapy. • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. • The continued use of DAPT (aspirin plus clopidogrel) for >90 days or the use of triple antiplatelet therapy is associated with excess risk of hemorrhage.

American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes**	Early hospital care- standard medical therapies
	• Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia.
	• Anti-ischemic and analgesic medications
	  ○ Nitrates
	  ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every five minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin.
	  ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension.

Clinical Guideline	Recommendations
(2014)[9]	▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue beta-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to beta-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of beta-clockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when beta-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke.

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	▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. ▪ Fibrinolytic therapy in patients with definite NSTE-ACS <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily.

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	• Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least two to four hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is

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	precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guideline for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2020)[10]**	<u>Pharmacological treatment of ischemia</u> • Sublingual or intravenous nitrates and early initiation of beta-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • Continuation of chronic beta-blocker therapy is recommended unless the patient is in overt heart failure • Sublingual or intravenous nitrates are recommended to relieve angina; intravenous treatment is recommended in patients with recurrent angina, uncontrolled hypertension, or signs of heart failure. • In patients with suspected/confirmed vasospastic angina, calcium channel blockers, and nitrates should be considered and beta-blockers avoided. <u>Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes</u> • Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150 to 300 mg (in aspirin-naïve patients) and a maintenance dose of 75 to 100 mg/day long-term regardless of treatment strategy. • A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risks of bleeds. o Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindication, for all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started). o Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. Prasugrel should be considered in preference to ticagrelor in NSTE-ACS patients who proceed to PCI. o Clopidogrel (300 to 600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or

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	who require oral anticoagulation. • $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after DES implantation may be considered in patients deemed at high bleeding risk. • Pre-treatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy. • It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known. • It is not recommended to administer prasugrel in patients whom coronary anatomy is not known. • GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications. • Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI. • It is not recommended to administer GPIIb/IIIa inhibitors in patients whom coronary anatomy is not known. • $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of the ischemic and bleeding risks of the patient. <u>Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes</u> • Parenteral anticoagulation is recommended at the time of diagnosis according to both ischemic and bleeding risks. • Fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy. • Bivalirudin is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI. • UFH is recommended in patients undergoing PCI who did not receive any anticoagulant. • In patients on fondaparinux undergoing PCI, a single intravenous bolus of UFH is recommended during the procedure. • Enoxaparin or UFH are recommended when fondaparinux is not available. • Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated for PCI with subcutaneous enoxaparin. • Additional activated clotting time-guided intravenous boluses of UFH during PCI may be considered following initial UFH treatment. • Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated. • Crossover between UFH and LMWH is not recommended. • In NSTEMI patients with no prior stroke/TIA and at high ischemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation. <u>Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation</u> • In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a $CHADS_2$-VASc score ≥ 2, recent VTE, mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. • An early invasive coronary angiography (within 24 hours) should be considered in moderate- to high-risk patients, irrespective of oral anticoagulant exposure, to expedite treatment allocation (medical vs PCI vs CABG) and to determine optimal antithrombotic regimen.

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	• Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to oral anticoagulation before coronary angiography is not recommended. • During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all non-vitamin K antagonist oral anticoagulants (NOACs) and if INR is <2.5 in VKA-treated patients. • Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. • Periprocedural DAPT administration consisting of aspirin and clopidogrel up to one week is recommended • Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months • Following coronary stenting, dual (oral) antiplatelet therapy (DAPT) including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with non-ST-elevation acute coronary syndromes and atrial fibrillation with a $CHADS_2$-VASc score of 1 (in males) or 2 (in females). • If at low bleeding risk (HAS-BLED ≤2), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for six months, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months. • If at high bleeding risk (HAS-BLED ≥3), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for one month, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months irrespective of the stent type. • Dual therapy with oral anticoagulant and clopidogrel may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis). • The use of ticagrelor or prasugrel as part of triple therapy is not recommended. • In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year. <u>Recommendations for post-interventional and maintenance treatment</u> • In patients with NSTE-ACS with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding. • Adding a second anti-thrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a moderate to high risk of ischemic events and without increased risk of major bleeding. • After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after three months should be considered • After stent implantation in patients undergoing DAPT, stopping aspirin after three to six months should be considered, depending on balance between ischemic and bleeding risk. • De-escalation of $P2Y_{12}$ inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.
American College of Cardiology Foundation/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[11]	<u>Antiplatelet therapy to support primary PCI for STEMI</u> • Aspirin 162 to 325 mg should be given before primary PCI. • After PCI, aspirin should be continued indefinitely. • A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg. • $P2Y_{12}$ inhibitor therapy should be given for one year to patients with STEMI who receive a stent (bare-metal or drug-eluting) during primary PCI using clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily. • It is reasonable to use 81 mg of aspirin per day in preference to higher

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	maintenance doses after primary PCI. • It is reasonable to start treatment with an IV GP IIb/IIIa receptor antagonist such as abciximab, high bolus-dose tirofiban or double-bolus eptifibatide at the time of primary PCI (with or without stenting or clopidogrel pre-treatment) in selected patients with STEMI who are receiving UFH. • It may be reasonable to administer IV GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended. • It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI. • Continuation of a $P2Y_{12}$ inhibitor beyond one year may be considered in patients undergoing drug-eluting stent placement. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. <u>Anticoagulant therapy to support primary PCI</u> • For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended: UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered or bivalirudin with or without prior treatment with UFH. • In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist. • Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis. <u>Adjunctive antiplatelet therapy with fibrinolysis</u> • Aspirin (162- to 325-mg loading dose) and clopidogrel (300 mg loading dose for ≤75 year of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy. • Aspirin should be continued indefinitely and clopidogrel (75 mg daily) should be continued for at least 14 days and up to one year in patients with STEMI who receive fibrinolytic therapy. • It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses after fibrinolytic therapy. <u>Adjunctive anticoagulant therapy with fibrinolysis</u> • Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the hospitalization, up to eight days or until revascularization if performed. • Recommended regimens include UFH administered as a weight-adjusted IV bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularization; enoxaparin administered according to age, weight, and creatinine clearance, given as an IV bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to eight days or until revascularization; or fondaparinux administered with initial IV dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 mL/min, for the duration of the index hospitalization, up to eight days or until revascularization. <u>Antiplatelet therapy to support PCI after fibrinolytic therapy</u> • After PCI, aspirin should be continued indefinitely.

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	• Clopidogrel should be provided as a 300 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy; a 600 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy; and a dose of 75 mg daily should be given after PCI. • After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses. • Prasugrel, in a 60 mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent. • Prasugrel, in a 10 mg daily maintenance dose, is reasonable after PCI. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. <u>Anticoagulant therapy to support PCI after fibrinolytic therapy</u> • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with IV UFH, additional boluses of IV UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior eight hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between eight and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given.

European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with Persistent ST-segment Elevation (2017)[12]**	<u>Periprocedural pharmacotherapy</u>
	• Platelet inhibition
	  ○ Patients undergoing primary percutaneous coronary intervention (PCI) should receive dual antiplatelet therapy (DAPT), a combination of aspirin and a $P2Y_{12}$ inhibitor, and a parenteral anticoagulant.
	  ○ A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.
	  ○ Aspirin (oral of intravenous if unable to swallow) is recommended as soon as possible for all patients without contraindications.
	  ○ GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.
	  ○ Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.
	• Anticoagulant therapy
	  ○ Anticoagulant options for primary PCI include unfractionated heparin (UFH), enoxaparin, and bivalirudin.
	  ○ Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.
	  ○ Routine use of UFH is recommended.
	  ○ In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.
	  ○ Routine use of enoxaparin intravenous should be considered.
	  ○ Routine use of bivalirudin should be considered.
	  ○ Fondaparinux is not recommended for primary PCI.
	
	<u>Maintenance antithrombotic strategy after ST-elevation myocardial infarction</u>

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	• Antiplatelet therapy with low-dose aspirin (75 to 100 mg) is indicated. • DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy should be considered for one to six months (according to a balance between the estimated risk of recurrent coronary events and bleeding). • DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding. • In patients with left ventricular (LV) thrombus, anticoagulation should be administered for up to six months guided by repeated imaging. • In high ischemic-risk patients who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice daily on top of aspirin for longer than 12 months may be considered for up to three years. • In low bleeding risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. <u>Routine therapies in the acute, subacute, and long-term phases</u> • Beta-blockers o Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF ≤40% unless contraindicated. o Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with no signs of acute heart failure, and with an SBP >120 mmHg. o Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindication. o Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia. • Lipid-lowering therapies o It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term. o An LDL-C goal of <70 mg/dL or a reduction of at least 50% if the baseline LDL-C is between 70 to 135 mg/dL is recommended. o It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation. o In patients with LDL-C ≥70 mg/dL despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. • ACE inhibitors/ARBs o ACE inhibitors are recommended, starting within the first 24 hours of

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	STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct. ○ An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors. ○ ACE inhibitors should be considered in all patients in the absence of contraindications. • Mineralocorticoid receptor antagonists ○ Mineralocorticoid receptor antagonists are recommended in patients with an LVEF ≤40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalemia.
American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions: **2021 Guideline for Coronary Artery Revascularization (2021)**[13]	Pharmacotherapy in Patients Undergoing PCI • In patients undergoing PCI, a loading dose of aspirin, followed by a daily dosing, is recommended to reduce ischemic events. • In patients with ACS undergoing PCI, a loading dose of $P2Y_{12}$ inhibitor, followed by daily dosing, is recommended to reduce ischemic events. • In patients with SIHD undergoing PCI, a loading dose of clopidogrel, followed by daily dosing is recommended to reduce ischemic events. • In patients undergoing PCI within 24 hours after fibrinolytic therapy, a loading dose of 300 mg of clopidogrel, followed by daily dosing, is recommended to reduce ischemic events. • In patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischemic events, including stent thrombosis. • In patients <75 years of age undergoing PCI within 24 hours after fibrinolytic therapy, ticagrelor may be a reasonable alternative to clopidogrel to reduce ischemic events. • In patients undergoing PCI who have a history of stroke or transient ischemic attack, prasugrel should not be administered. Antiplatelet Pharmacotherapy in Patients Undergoing CABG • In patients undergoing CABG who are already taking daily aspirin preoperatively, it is recommended that they continue taking aspirin until the time of surgery to reduce ischemic events. • In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours before surgery to reduce major bleeding complications. • In patients undergoing CABG, discontinuation of short-acting glycoprotein IIb/IIIa inhibitors for four hours and abciximab for 12 hours before surgery is recommended to reduce the risk of bleeding and transfusion. • In patients undergoing elective CABG who receive $P2Y_{12}$ receptor inhibitors before surgery, it is reasonable to discontinue clopidogrel for five days, ticagrelor for three days and prasugrel for seven days before CABG to reduce risk of major bleeding and blood product transfusion. • In patients undergoing elective CABG who are not already taking aspirin, the initiation of aspirin in the immediate pre-operative period is not recommended. Antiplatelet Pharmacotherapy in Patients After Revascularization • In selected patients undergoing PCI, shorter duration dual antiplatelet therapy (one to three months) is reasonable, with subsequent transition to $P2Y_{12}$ inhibitor monotherapy to reduce the risk of bleeding events. • In patients undergoing CABG, aspirin (100 to 325 mg daily) should be initiated within six hours postoperatively and then continued indefinitely to

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	reduce the occurrence of SVG closure and adverse cardiovascular events. • In selected patients undergoing CABG, dual antiplatelet therapy with aspirin and ticagrelor or clopidogrel for one year may be reasonable to improve vein graft patency compared with aspirin alone. • In patients with atrial fibrillation who are undergoing PCI and are taking oral anticoagulant therapy, it is recommended to discontinue aspirin treatment after one to four weeks while maintaining $P2Y_{12}$ inhibitors in addition to a non-vitamin K oral anticoagulant (rivaroxaban, dabigatran, apixaban or edoxaban) or warfarin to reduce the risk of bleeding. • In patients with atrial fibrillation who are undergoing PCI, are taking oral anticoagulant therapy, and are treated with DAPT or a $P2Y_{12}$ inhibitor monotherapy, it is reasonable to choose a non-vitamin K oral anticoagulant over warfarin to reduce the risk of bleeding.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)[14]**	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u>

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	• For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.
	• Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.
	• For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
	• For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk.
	
	<u>Adults with high blood cholesterol</u>
	• In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended.
	• In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more.
	• In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.
	• In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.
	• In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.
	• In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy.
	• In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND
	  ○ If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking);
	  ○ If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age;
	  ○ If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy.
	• In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy.
	
	<u>Adults with high blood pressure or hypertension</u>
	• In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include:
	  ○ weight loss;

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	○ a heart-healthy dietary pattern; ○ sodium reduction; ○ dietary potassium supplementation; ○ increased physical activity with a structured exercise program; and ○ limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
National Institute for Health and Clinical Excellence: **Clopidogrel and Modified-Release Dipyridamole for the Prevention of Occlusive**	• This guidance applies to people who have had an occlusive vascular event, or who have established peripheral arterial disease. This guidance does not apply to people who have had, or are at risk of, a stroke associated with AF, or who need treatment to prevent occlusive events after coronary revascularization or carotid artery procedures. • For people who have had an ischemic stroke, clopidogrel is recommended as a treatment option. For people who have a contraindication or intolerance to

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Vascular Events (2010)[15]	clopidogrel, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to both clopidogrel and aspirin, modified-release dipyridamole alone is recommended as a treatment option. • For people who have had a TIA, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to aspirin, modified-release dipyridamole alone is recommended as a treatment option. • For people who have had a MI, clopidogrel is recommended only when treatment with aspirin is contraindicated or not tolerated. • For people with peripheral arterial disease, clopidogrel is recommended as a treatment option. • For people with multi-vascular disease, clopidogrel is recommended as a treatment option. • Treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2014)[16]**	<u>Medical therapy to prevent MI and death in patients with stable IHD</u> • Aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications. • Treatment with clopidogrel is a reasonable option when aspirin in contraindicated. • Dipyridamole should not be used as antiplatelet therapy. • Beta-blocker therapy should be initiated and continued for three years in all patients with normal left ventricular (LV) function following MI or acute coronary syndromes. • Metoprolol succinate, carvedilol, or bisoprolol should be used for all patients with systolic LV dysfunction (ejection fraction ≤40%) with heart failure or prior MI, unless contraindicated. • ACE inhibitors should be prescribed in all patients with stable IHD who also have hypertension, diabetes, LV systolic dysfunction (ejection fraction ≤40%), and/or chronic kidney disease, unless contraindicated. • Angiotensin-receptor blockers (ARBs) are recommended for patients with stable IHD who have hypertension, diabetes, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. • Patients should receive an annual influenza vaccine. <u>Medical therapy for relief of symptoms in patients with stable IHD</u> • Beta-blockers are recommended as initial therapy for relief of symptoms. • Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects. • Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful. • Nitroglycerin or nitroglycerin spray should be used for immediate relief of angina. • Ranolazine is a fourth-line agent reserved for patients who have contraindications to, do not respond to, or cannot tolerate β-blockers, calcium-channel blockers, or long-acting nitrates.
European Society of Cardiology: **Guidelines for the Diagnosis and**	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u> • The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events. • Optimal medical treatment indicates at least one drug for angina/ischaemia

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Management of Chronic Coronary Syndromes (2019)[17]	relief plus drugs for event prevention. • It is recommended to educate patients about the disease, risk factors and treatment strategy. • It is indicated to review the patient's response soon after starting therapy. • Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding. • Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended • ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events • Angina/ischemia relief: o Short-acting nitrates are recommended. o First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms o o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. • Event prevention: o Low-dose aspirin daily is recommended in all stable CAD patients. o Clopidogrel is indicated as an alternative in case of aspirin intolerance. o Statins are recommended in all stable CAD patients. o It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes). <u>Treatment in patients with microvascular angina</u> • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • ß-blockers are recommended as a first-line treatment. • Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT).

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	• Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only. • Platelet function testing or genetic testing may be considered in specific or high risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after 2nd generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.

American Heart Association/American College of Cardiology Foundation: **Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and Other Atherosclerotic**	<u>Antiplatelet agents/anticoagulants</u>
	• Aspirin 75 to 162 mg daily is recommended in all patients with coronary artery disease unless contraindicated.
	  ◦ Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.
	  ◦ Combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease.
	• A $P2Y_{12}$ receptor antagonist in combination with aspirin is indicated in

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Vascular Disease: 2011 Update (2011)[18]	patients after ACS or PCI with stent placement. • For patients receiving a bare-metal stent or drug-eluting stent during PCI or ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily or ticagrelor 90 mg twice daily should be given for at least 12 months. • If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy after stent implantation, earlier discontinuation (e.g., 12 months) is reasonable. The risk for serious cardiovascular events because of early discontinuation of thienopyridines is greater for patients with drug-eluting stents than those with bare-metal stents. • After PCI, it is reasonable to use aspirin 81 mg daily in preference to higher maintenance doses. • For patients undergoing CABG, aspirin should be started within six hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg daily for one year appear to be efficacious. • For patients undergoing CABG, clopidogrel (75 mg daily) is a reasonable alternative in patients who are intolerant of or allergic to aspirin. • In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75 to 325 mg daily), clopidogrel alone (75 mg daily) or the combination of aspirin plus dipyridamole ER (25 mg and 200 mg twice daily, respectively) should be started and continued. • For patients with symptomatic atherosclerotic PAD of the lower extremity, antiplatelet therapy with aspirin (75 to 325 mg daily) or clopidogrel (75 mg daily) should be started and continued. • The benefits of aspirin in patients with asymptomatic PAD of the lower extremities are not well established. • Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other VKA to treat patients with atherosclerosis. • If there is a compelling indication for anticoagulant therapy, such as AF, prosthetic heart valve, left ventricular thrombus or concomitant venous thromboembolic disease, warfarin should be administered in addition to the low-dose aspirin (75 to 81 mg daily). • For patients requiring warfarin, therapy should be administered to achieve the recommended INR for the specific condition. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.
European Association for Cardiovascular Prevention and Rehabilitation: **European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2021)[19]**	<u>Antiplatelet therapy</u> • Antiplatelet therapy is not recommended in individuals free from cardiovascular disease (CVD), due to the increased risk of major bleeding. • In patients with ischemic stroke or transient ischemic attack (TIA), prevention with antithrombotics is recommended. If the event is a non-cardioembolic ischemic stroke or TIA use of antiplatelets is recommended. If the event is a cardioembolic stroke or TIA use of anticoagulants is recommended. • In acute coronary syndromes, a $P2Y_{12}$ inhibitor for 12 months is recommended in addition to aspirin, unless there are contraindications such as excessive risk of bleeding. • $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after drug-eluting stent (DES) implantation may be considered in patients deemed at high bleeding risk. • In patients with chronic coronary syndrome, clopidogrel 75 mg daily is recommended, in addition to aspirin for six months following stenting. Shorter duration considered if increased risk or occurrence of life-threatening bleeding.

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	• $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of ischemic and bleeding risks of the patient. • In the chronic phase (>12 months) after myocardial infarction (MI), aspirin is recommended. • In patients with non-cardioembolic ischemic stroke or transient ischemic attack (TIA), prevention with aspirin only, or dipyridamole plus aspirin or clopidogrel alone is recommended. • In patients with minor ischemic stroke or TIA, DAPT with aspirin and clopidogrel or with aspirin and ticagrelor, for three weeks after event should be considered • Prasugrel is not recommended in patients with stable coronary artery disease (CAD). Ticagrelor is not recommended in patients with stable CAD without a previous acute coronary syndrome (ACS). • Antiplatelet therapy is recommended in patients with symptomatic lower extremity artery disease.
The American College of Cardiology/ American Heart Association: **Practice Guidelines for the Management of Patients with Peripheral Artery Disease (2013)**[20]	<u>Exercise and lower extremity peripheral artery disease (PAD) rehabilitation</u> • A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. • Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times/week for a minimum of 12 weeks. • The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication. <u>Smoking cessation</u> • Patients who are smokers or former smokers should be asked about status of tobacco use at every visit. Patients with lower extremity PAD who use tobacco should be advised to stop smoking. • Patients should be provided with counseling and assistance with developing a plan for smoking cessation. • One or more of the following pharmacological therapies should be offered if not contraindicated: varenicline, bupropion and nicotine replacement therapy. <u>Antiplatelet and antithrombotic drugs</u> • Antiplatelet therapy is indicated to reduce the risk of MI, stroke and vascular death in patients with symptomatic atherosclerotic lower extremity PAD and in asymptomatic patients with ankle brachial index ≤0.90. The usefulness of antiplatelet therapy is not well established in asymptomatic patients with ankle brachial index between 0.91 and 0.99. • Aspirin (75 to 325 mg/day) is recommended to reduce the risk of cardiovascular events. Clopidogrel (75 mg/day) is recommended as an alternative to aspirin. • Combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD who are at high cardiovascular risk and not at increased risk of bleeding. • The addition of warfarin to antiplatelet therapy is of no proven benefit and is potentially harmful due to increased risk of major bleeding. <u>Medical and pharmacological treatment for claudication</u> • Cilostazol (100 mg orally twice daily) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure). • A therapeutic trial of cilostazol should be considered in all patients with

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	lifestyle-limiting claudication (in the absence of heart failure). • Pentoxifylline (400 mg three times daily) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication. • The clinical effectiveness of pentoxifylline as therapy for intermittent claudication is marginal and not well established. • The effectiveness of L-arginine for patients with intermittent claudication is not well established. • The effectiveness of propionyl L-carnitine as a therapy to improve walking distance in patients with intermittent claudication is not well established. • The effectiveness of ginkgo biloba as a therapy to improve walking distance in patients with intermittent claudication is not well established. • Oral vasodilator prostaglandins such as beraprost* and iloprost are not effective medications to improve walking distance in patients with intermittent claudication. • Vitamin E is not recommended as a treatment for patients with intermittent claudication. • Chelation (e.g. ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects.
American College of Cardiology/American Heart Association: **Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease (2016)**[21]	<u>Recommendations for Antiplatelet Agents:</u> • Antiplatelet therapy with aspirin alone (range 75 to 325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce myocardial infarction (MI), stroke, and vascular death in patients with symptomatic peripheral artery disease (PAD). • In asymptomatic patients with PAD (Ankle Brachial Index (ABI) ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death. • In asymptomatic patients with borderline ABI (0.91 to 0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain. • The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established. • DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization. • The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain. <u>Recommendations for Statin Agents:</u> • Treatment with a statin medication is indicated for all patients with PAD. <u>Recommendations for Antihypertensive Agents:</u> • Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death. • The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD. <u>Recommendations for Smoking Cessation:</u> • Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit. • Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, bupropion,

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	and/or nicotine replacement therapy) and/or referral to a smoking cessation program. • Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places. <u>Recommendations for Glycemic Control:</u> • Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team. • Glycemic control can be beneficial for patients with critical limb ischemia (CLI) to reduce limb-related outcomes. <u>Recommendations for Oral Anticoagulation:</u> • The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain. • Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD. <u>Recommendations for Cilostazol:</u> • Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication. <u>Recommendations for Pentoxifylline:</u> • Pentoxifylline is not effective for treatment of claudication.
European Society of Cardiology, Task Force on the Use of Antiplatelet Agents in Patients With Atherosclerotic Cardiovascular Disease: **Expert Consensus Document on the Use of Antiplatelet Agents (2004)**[22]	<u>Major recommendations for individual antiplatelet agents</u> Aspirin: • Aspirin once-daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. • Because of gastrointestinal toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting. • The available evidence supports daily doses of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients (e.g., ≥3% per annum). • In clinical situations where an immediate antithrombotic effect is required (such as in ACS or in acute ischemic stroke), a loading dose of 160 to 300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of thromboxane A2-dependent platelet aggregation. • No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient. • The routine use of proton pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75 to 100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting. • Nonsteroidal anti-inflammatory drugs have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin. • Because of potential pharmacodynamic interactions between traditional nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) and aspirin, patients treated with low-dose aspirin requiring nonsteroidal ant-inflammatory drug therapy may benefit from the use of selective cyclooxegenase-2 inhibitors. Ticlopidine: • The role of ticlopidine in the present therapeutic armamentarium is uncertain. • Although there are no large head-to-head comparisons between the two thienopyridines, indirect comparisons are highly suggestive of a lower burden

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	of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine. • In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent MI. Clopidogrel: • Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain and the drug has not been granted a claim of "superiority" vs aspirin by regulatory authorities. • Clopidogrel 75 mg/day is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a contraindication to low-dose aspirin. • The results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial have led to Food and Drug Administration approval of a new indication for clopidogrel in patients with NSTE ACS. A loading dose of 300 mg clopidogrel should be used in this setting, followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of PCI, length of clopidogrel treatment and combination with GP IIb/IIIa antagonists. Dipyridamole: • Although the combination of low-dose aspirin and dipyridamole ER (200 mg twice-daily) is considered an acceptable option for initial therapy of patients with noncardioembolic cerebral ischemic events, there is no basis to recommend this combination in patients with ischemic heart disease.
European Society of Cardiology/ European Association for Cardio-Thoracic Surgery: **2017 Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease (2017)**[23]	<u>Recommendations on $P2Y_{12}$ inhibitor selection and timing</u> • In patients with acute coronary syndrome (ACS), ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications. • In patients with ACS undergoing percutaneous coronary intervention (PCI), prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) or initially conservatively managed ST-elevation myocardial infarction (STEMI) if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high risk of life-threatening bleeding or other contraindications. • Pre-treatment with a $P2Y_{12}$ inhibitor is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made as well as in patients with STEMI. • In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established. • In patients with stable coronary artery disease (CAD), pre-treatment with clopidogrel may be considered if the probability of PCI is high. • Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for an oral anticoagulant. • Clopidogrel (300 mg loading dose in patients aged <75, 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis. • Ticagrelor or prasugrel on top of aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI, taking into account the ischemic (e.g. high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding (e.g. according to PRECISE-DAPT score) risks.

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	• In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel. <u>Switching between oral $P2Y_{12}$ inhibitors</u> • In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindications to ticagrelor exist. • Additional switching between oral $P2Y_{12}$ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms. <u>Measures to minimize bleeding while on dual antiplatelet therapy</u> • Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator. • In patients treated with DAPT, a daily aspirin dose of 75 to 100 mg is recommended. • A proton pump inhibitor in combination with DAPT is recommended. • Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended. <u>Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention</u> • In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT $\geq$25). <u>Dual antiplatelet therapy duration in patients with acute coronary syndrome undergoing medical therapy management</u> • In patients with ACS who are managed with medical therapy alone and treated with DAPT, it is recommended to continue $P2Y_{12}$ inhibitor therapy (either ticagrelor or clopidogrel) for 12 months. • Ticagrelor is recommended over clopidogrel, unless the bleeding risk outweighs the potential ischemic benefit. • Prasugrel is not recommended in medically managed ACS patients. <u>Dual antiplatelet therapy in patients undergoing elective cardiac and non-cardiac surgery</u> • It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively. • It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)[24]**	<u>Pharmacological treatments indicated in patients with New York Heart Association (NYHA) Class II-IV heart failure with reduced ejection fraction</u> • An angiotensin-converting enzyme (ACE) inhibitor is recommended, in addition to a beta-blocker, for symptomatic patients with heart failure with reduced ejection fraction (HFrEF) to reduce the risk of heart failure (HF) hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin

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	are recommended, in addition to optimal medical therapy with an ACE inhibitor/angiotensin receptor neprilysin inhibitor (ARNI), a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with left ventricle ejection fraction (LVEF) ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor or angiotensin receptor blocker (ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a beta-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated left ventricle in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a beta-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.

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	• Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin are recommended in patients with diabetes at high risk • of CV disease or with CV disease in order to prevent HF hospitalizations. • Counseling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and systolic blood pressure (SBP) >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with low molecular weight heparin) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the vasodilating agents, miscellaneous 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 Vasodilating Agents, Miscellaneous [1-4]

Indication	Dipyridamole	Vericiguat	Aspirin and Dipyridamole
Atherothrombotic/Vascular Events			
Reduce the rate of MI and stroke in patients with established peripheral arterial disease or with a history of recent MI or recent stroke			
Reduce postoperative thromboembolic complications of cardiac valve replacement as an adjunct to coumarin anticoagulants	✔ (tablet)		
Ischemic Stroke or Transient Ischemic Attack			
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis			✔
Miscellaneous Indications			
Radionuclide myocardial perfusion study	✔ (injection)		
Reduce the risk of cardiovascular death and heart failure hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics in adults with symptomatic chronic heart failure and ejection fraction <45%		✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the vasodilating agents, miscellaneous are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Vasodilating Agents, Miscellaneous [2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Dipyridamole	37 to 66	99	Liver (% not reported)	Renal (% not reported)	40 minutes (alpha), 10 hours (beta)*
Vericiguat	93	98	Liver (% not reported)	Renal (53) Feces (45)	30

*Dipyridamole follows a two-compartment model.

V. Drug Interactions

Major drug interactions with the vasodilating agents, miscellaneous are listed in Table 5. Concurrent use of these agents with non-steroidal anti-inflammatory drugs (NSAIDS) increases bleeding risk.[2]

Table 5. Major Drug Interactions with the Vasodilating Agents, Miscellaneous [2]

Generic Name(s)	Interaction	Mechanism
Dipyridamole	Defibrotide	Concomitant use of defibrotide and a systemic antithrombotic agent is contraindicated as the pharmacodynamic activity of the antithrombotic agent may be enhanced, leading to an increased risk of bleeding.
Dipyridamole	SSRIs	Concurrent use may result in an increased risk of bleeding.
Vericiguat	Riociguat	Concurrent use of vericiguat and other soluble guanylate cyclase stimulators may result in additive effects due to duplication of therapy.

VI. Adverse Drug Events

The most common adverse drug events reported with the vasodilating agents, miscellaneous are listed in Table 6. The boxed warnings are listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Vasodilating Agents, Miscellaneous [1-7,13]

Adverse Events	Dipyridamole	Vericiguat	Aspirin and Dipyridamole
Cardiovascular			
Angina pectoris	✔	-	<1
Arrhythmia	-	-	<1
Cardiac failure	-	-	2
Hypertension	-	16	-
Hypotension	✔	-	-
Palpitation	✔	-	-
Syncope	-	-	1
Tachycardia	✔	-	-
Central Nervous System			
Amnesia	-	-	2
Cerebral edema	-	-	<1
Cerebral hemorrhage	-	-	<1
Coma	-	-	<1
Confusion	-	-	1
Dizziness	14	-	-
Fatigue	-	-	6
Flushing	✔	-	-
Headache	2	-	38
Lethargy/malaise	✔	-	2
Pain	-	-	6
Seizure	-	-	2
Somnolence	-	-	1
Dermatologic			
Alopecia	✔	-	<1
Purpura	-	-	1
Pruritus	✔	-	<1
Rash	2	-	<1
Ulceration	-	-	<1
Urticaria	-	-	<1
Endocrine and Metabolic			

Adverse Events	Dipyridamole	Vericiguat	Aspirin and Dipyridamole
Pancreatitis	-	-	<1
Gastrointestinal			
Abdominal distress	6	-	-
Abdominal pain	-	-	18
Anorexia	-	-	1
Bleeding	-	-	4
Diarrhea	✔	-	13
Dyspepsia	✔	-	>10
Gastrointestinal hemorrhage	-	-	1
Hematemesis	-	-	<1
Hemorrhoids	-	-	1
Nausea	✔	-	16
Rectal bleeding	-	-	2
Vomiting	✔	-	8
Genitourinary			
Interstitial nephritis	-	-	<1
Papillary necrosis	-	-	<1
Renal failure	-	-	<1
Uterine hemorrhage	-	-	<1
Hematologic			
Anemia	-	10	2
Aplastic anemia	-	-	<1
Disseminated intravascular coagulation	-	-	<1
Pancytopenia	-	-	<1
Prothrombin time prolonged	-	-	<1
Thrombocytopenia	✔	-	<1
Hepatic			
Cholelithiasis	✔	-	<1
Hepatic failure	-	-	<1
Hepatitis	✔	-	<1
Jaundice	-	-	<1
Liver dysfunction	✔	-	-
Musculoskeletal			
Arthralgia	-	-	6
Arthritis	✔	-	2
Arthrosis	-	-	1

Adverse Events	Dipyridamole	Vericiguat	Aspirin and Dipyridamole
Back pain	-	-	5
Fatigue	✔	-	-
Myalgia	✔	-	1
Paresthesia	✔	-	<1
Rhabdomyolysis	-	-	<1
Weakness	-	-	2
Respiratory			
Bronchospasm	-	-	<1
Cough	-	-	2
Dyspnea	-	-	<1
Epistaxis	-	-	2
Hemoptysis	-	-	<1
Larynx edema	✔	-	-
Pulmonary edema	-	-	<1
Tachypnea	-	-	<1
Upper respiratory infection	-	-	1
Other			
Allergic reaction	-	-	<1
Anaphylactoid reaction/anaphylaxis	-	-	<1
Angioedema	-	-	<1
Ante-/peri-/postpartum bleeding	-	-	<1
Deafness	-	-	<1
Hypersensitivity reaction	✔	-	-
Lower weight infants	-	-	<1
Reye's syndrome	-	-	<1
Stillbirths	-	-	<1

✔ Percent not specified.
- Event not reported.

Table 7. Boxed Warning for Vericiguat[3]

WARNING
Females of reproductive potential: Exclude pregnancy before the start of treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment. Do not administer vericiguat to a pregnant female because it may cause fetal harm.

VII. Dosing and Administration

The usual dosing regimens for the vasodilating agents, miscellaneous are listed in Table 8.

Table 8. Usual Dosing Regimens for the Vasodilating Agents, Miscellaneous [14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Dipyridamole	Cardiac valve replacement, adjunct prophylaxis: Tablet: 75 to 100 mg four times daily as an adjunct to warfarin therapy Radionuclide myocardial perfusion study: Injection: 0.142 mg/kg/min (0.57 mg/kg total) intravenously over four minutes prior to thallium; maximum 60 mg	Safety and efficacy in children below the age of 12 years have not been established.	Injection: 5 mg/mL Tablet: 25 mg 50 mg 75 mg
Vericiguat	Heart failure: Tablet: initial, 2.5 mg once daily; maintenance, double the dose every two weeks to reach target dose of 10 mg once daily, as tolerated.	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg 10 mg
Combination Products			
Aspirin and dipyridamole	Thromboembolic stroke, recurrent, prophylaxis: Capsule: 25-200 mg twice daily Alternative regimen for patients with intolerable headaches: 25-200 mg at bedtime and low-dose aspirin in the morning; return to usual dose as soon as tolerance to headache develops (usually within a week)	Safety and efficacy in children have not been established.	Capsule (IR aspirin-ER dipyridamole): 25-200 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the vasodilating agents, miscellaneous are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Vasodilating Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cerebrovascular Conditions				
Johnston et al.[25] (2020) Ticagrelor 180 mg loading dose then 90 mg twice daily maintenance + aspirin 300 to 325 mg loading dose then 75 to 100 mg once daily maintenance vs placebo + aspirin 300 to 325 mg loading dose then 75 to 100 mg once daily maintenance	DB, MC, PC, RCT Patients > 40 years of age who had mild-to-moderate acute noncardioembolic ischemic stroke or high-risk TIA	N=11,016 30 days	Primary: Composite of stroke or death Secondary: First subsequent stroke and disability measured on the Rankin scale, safety	Primary: Death or stroke occurred in 303 patients in the ticagrelor–aspirin group (5.5%) and in 362 patients in the aspirin group (6.6%) (HR, 0.83; 95% CI, 0.71 to 0.96; P=0.02). Secondary: Subsequent ischemic stroke, occurred in 276 patients in the ticagrelor–aspirin group (5.0%) and in 345 patients in the aspirin group (6.3%) (HR, 0.79; 95% CI, 0.68 to 0.93; P=0.004). Overall disability (score >1 on the modified Rankin scale) occurred in 23.8% of the patients in the ticagrelor–aspirin group and in 24.1% of the patients in the aspirin group (OR, 0.98; 95% CI, 0.89 to 1.07; P=0.61). Severe bleeding, as defined according to the GUSTO criteria (the primary safety outcome event), occurred in 28 patients (0.5%) in the ticagrelor–aspirin group and in seven patients (0.1%) in the aspirin group (HR, 3.99; 95% CI, 1.74 to 9.14; P=0.001).
International Stroke Trial[26] (1997) Aspirin 300 mg/day vs heparin 5,000 or 12,500 IU BID vs	MC, OL, RCT Patients with acute ischemic stroke (randomized within 48 hours of stroke onset), 61% of patients were >70 years	N=19,435 Up to 14 days	Primary: Death from any cause within 14 days, death or dependency at six months Secondary: Symptomatic intracranial or extracranial hemorrhage,	Primary: Aspirin-allocated patients experienced slightly fewer deaths within 14 days (9.0 vs 9.4%; P value not significant). There was a trend toward a reduction in death or dependence at six months (62.2 vs 63.5%; P=0.07; a difference of 13 per 1,000 patients) and after adjustment for baseline prognosis the benefit from aspirin was significant (P=0.03; a difference of 14 per 1,000 patients). More aspirin-allocated patients reported complete recovery from their stroke (17.6 vs 16.6%; P=0.07). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin and heparin vs placebo			ischemic stroke or other major event within 14 days	Aspirin-allocated patients had significantly fewer recurrent ischemic strokes within 14 days (2.8 vs 3.9%; P<0.001) with no significant excess of hemorrhagic strokes (0.9 vs 0.8%), so the reduction in death or nonfatal recurrent stroke with aspirin was significant (11.3 vs 12.4%; P=0.02; 11 fewer per 1,000 patients treated). Aspirin was associated with a significant excess of 5 transfused or fatal extracranial bleeds per 1,000 patients (1.1 vs 0.6%; P=0.0004), in the absence of heparin the excess was two and was not significant. There was no interaction between aspirin and heparin in the main outcomes.
CAST[27] (1997) Aspirin 160 mg/day vs placebo	MC, PC, RCT Hospitalized patients with acute ischemic stroke (were randomized within 48 hours of stroke onset), mean age 63 years	N=21,106 Up to 4 weeks	Primary: Death from any cause during the four week treatment period, death or dependence at discharge Secondary: Fatal or nonfatal recurrent stroke, death or nonfatal stroke during the scheduled treatment period	Primary: Patients in the aspirin group experienced a small but significant reduction in both early mortality (3.3 vs 3.9%; P=0.04) and recurrent ischemic strokes (1.6 vs 2.1%; P=0.01) but slightly more hemorrhagic strokes than placebo (1.1 vs 0.9%; P>0.1). At discharge, the aspirin-treated group experienced a smaller proportion of patients who were dead or dependent (30.5 vs 31.6%; P=0.08), corresponding to 11.4 fewer per 1,000 patients. Secondary: Fatal and nonfatal recurrent strokes occurred in 3.2% of aspirin-allocated patients vs 3.4% for placebo (P value not significant). For the combined in hospital end point of death or nonfatal stroke at four weeks, there was a 12% proportional risk reduction with aspirin (5.3 vs 5.9%; P=0.03), an absolute difference of 6.8 fewer cases per 1,000 patients.
Diener et al.[28] (1996) ESPS 2 Aspirin 25 mg BID vs	DB, MC, PC, RCT Male and female patients who had an ischemic stroke (76%) or TIA (24%) within three months	N=6,602 24 months	Primary: Stroke (fatal or nonfatal), death (all-cause mortality), combined stroke or death	Primary: In comparison to placebo, stroke risk was reduced by 18% with aspirin alone (P=0.013), 37% with the fixed-dose combination product of aspirin and ER dipyridamole (P<0.001) and 16% with dipyridamole alone (P=0.039). There was no significant difference in all-cause mortality among the active

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin and dipyridamole ER 25-200 mg BID (Aggrenox®) vs dipyridamole ER* 200 mg BID vs placebo	prior to study entry, mean age 66.7 years		Secondary: TIA, adverse events	treatment groups. In comparison to placebo, the risk of stroke or death was reduced by 13% with aspirin alone (P=0.016), 24% with the fixed-dose combination (P<0.001) and 15% with dipyridamole alone (P=0.015). Secondary: Aspirin alone (P<0.001), the fixed-dose combination product (P<0.001) and dipyridamole alone (P<0.01) were significantly effective in preventing TIA compared to placebo. Headache was the most common adverse event, occurring more frequently in the dipyridamole-treated patients. All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received aspirin in comparison to placebo or dipyridamole.
Leonardi-Bee et al.[29] (2005) Aspirin and dipyridamole vs dipyridamole vs aspirin vs control Two formulations of dipyridamole were assessed: conventional (daily	MA (5 trials) Patients with previous ischemic stroke and/or TIA	N=11,036 15 to 72 months	Primary: Incidence of combined fatal and nonfatal stroke Secondary: Nonfatal stroke; combined fatal and nonfatal MI; vascular death; composite of nonfatal stroke, nonfatal MI and vascular death	Primary: The incidence of recurrent stroke was reduced by dipyridamole as compared to control (OR, 0.82; 95% CI, 0.68 to 1.00; P<0.05), and by combined aspirin and dipyridamole vs aspirin alone (OR, 0.78; 95% CI, 0.65 to 0.93; P<0.05), dipyridamole alone (OR, 0.74; 95% CI, 0.60 to 0.90; P<0.05), or control (OR, 0.61; 95% CI, 0.51 to 0.71; P<0.05). Secondary: The combination of dipyridamole and aspirin also significantly reduced the composite outcome of nonfatal stroke, nonfatal MI, and vascular death as compared to aspirin alone (OR, 0.84; 95% CI, 0.72 to 0.97; P<0.05), dipyridamole alone (OR, 0.76; 95% CI, 0.64 to 0.90; P<0.05), or control (OR, 0.66; 95% CI, 0.57 to 0.75; P<0.05). The combination of dipyridamole and aspirin significantly reduced the incidence of fatal and nonfatal MI compared to control (P<0.05) but not compared to monotherapy with aspirin or dipyridamole (P>0.05). Vascular death was not altered in any group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose 150 to 300 mg) and modified release (daily dose 400 mg). The daily dose of aspirin was 50 to 1,300 mg.				
Sacco et al.[30] (2005) Aspirin and dipyridamole ER 25-200 mg BID (Aggrenox®) vs aspirin 25 mg BID	DB, MC, PC, RCT (Post-hoc analysis of the ESPS 2 trial) Male and female patients who had an ischemic stroke (76%) or TIA (24%) within three months prior to study entry, mean age 66.7 years	N=1,650 (Aggrenox®) N=1,649 (aspirin) Duration not specified	Primary: Rates of annual strokes and combined strokes and vascular events Secondary: Not reported	Primary: Compared to aspirin alone, aspirin plus ER dipyridamole was more effective in reducing the risk of stroke (relative risk reduction, 23%; P=0.006) and stroke or vascular events (relative risk reduction, 22%, P=0.003). A more pronounced efficacy was observed for patients <70 years; those with hypertension, prior MI, prior stroke or TIA, and any prior cardiovascular disease; and smokers (P<0.01 for all). The greatest relative hazard reduction (44.6%) was noted for patients with a stroke or TIA before the qualifying event. Significant hazard reductions were reported for the combined outcome of stroke or vascular events with the greatest reductions found in patients with prior stroke or TIA, previous MI and among current smokers. The difference in efficacy increased in higher-risk patients. Secondary: Not reported
ESPRIT Study Group[31] (2006) ESPRIT Aspirin (30 to 325 mg/day) and dipyridamole ER (200 mg BID), either as a fixed-dose combination or	MC, OL, RCT Patients with a TIA or minor stroke	N=2,739 3.5 years (mean follow-up)	Primary: Composite of death from all vascular causes, nonfatal stroke, nonfatal MI or major bleeding complication (whichever happened first) Secondary:	Primary: Primary outcome events occurred in 173 (13%) of patients on aspirin plus dipyridamole vs 216 (16%) on aspirin monotherapy (HR, 0.80; 95% CI, 0.66 to 0.98; absolute risk reduction, 1.0% per year; 95% CI, 0.1 to 1.8). Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs 184), mainly because of headache. Secondary: The HRs for death from all causes and all vascular causes were 0.88 (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
individual components vs aspirin 30 to 325 mg/day			Death from all causes, death from all vascular causes, death from all vascular causes and nonfatal stroke, all major ischemic events, all vascular events, major bleeding complications	CI, 0.67 to 1.17) and 0.75 (95% CI, 0.51 to 1.10). Ischemic events were less frequent in the combination group than in the monotherapy group (HR, 0.81; 95% CI, 0.65 to 1.01). Major bleeding complications arose in 35 patients allocated to aspirin and dipyridamole vs 53 patients allocated to aspirin alone, whereas minor bleeding was reported in 171 patients allocated to the combination regimen vs 168 patients allocated to aspirin (RR, 1.03; 95% CI, 0.84 to 1.25).
Uchiyama et al.[32] (2011) JASAP Aspirin and dipyridamole ER 25 to 200 mg BID vs aspirin 81 mg QD Concomitant use of anticoagulation and antiplatelet therapies was prohibited.	AC, DB, MC, PG, RCT Patients ≥50 years of age with an ischemic stroke ≥1 week (but no more than six months) prior to enrollment, with ≥2 additional risk factors, stable neurological signs and symptoms, and responsible lesion confirmed by CT or MRI	N=1,294 12 months	Primary: Recurrent ischemic stroke (fatal or nonfatal) Secondary: Cerebral hemorrhage; subarachnoid hemorrhage; TIA; ACS; other vascular events; composite of ischemic stroke, TIA, MI, unstable angina, or sudden death attributable to thromboembolism; stroke (composite of ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage); safety	Primary: Recurrent ischemic stroke occurred in 6.9 (n=45) and 5.0% (n=32) of patients receiving combination therapy and aspirin, respectively. Noninferiority of combination therapy compared to aspirin was not shown (HR, 1.47; 95% CI, 0.93 to 2.31). Results were consistent in the per protocol population. Secondary: The event rate of stroke was significantly higher with combination therapy compared to aspirin. There was no difference between the two treatments for any other secondary endpoint. Combination therapy and aspirin were both well tolerated. There was a significantly higher total number of adverse events with combination therapy (640 vs 611; P=0.04). The difference in drug-related adverse events was mainly due to headache in the early stages of treatment with combination therapy. More patients receiving combination therapy discontinued treatment because of headache. Major bleeding events and clinically relevant minor bleeding events were comparable between the two treatments. No relevant changes in laboratory parameters, vital signs, and electrocardiography were noted with either treatment. There were four (0.6%) and 10 (1.6%) deaths with combination therapy and aspirin. A multivariate analysis taking into account potential confounders for

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			A post hoc analysis was performed evaluating the event rate of intracranial hemorrhage and the composite of stroke or major bleeding for different subgroups	recurrence of ischemic stroke but only keeping covariates with a significant contribution in the model revealed a similar result for the comparison between treatments as the primary analysis. The analysis also revealed that higher modified Rankin Scale values and established end organ damage at baseline had a deleterious effect on the primary outcome, whereas the concomitant therapy with statins had a beneficial effect.
Verro et al.[33] (2008) Aspirin and dipyridamole (IR and ER formulations) vs aspirin	MA (6 trials) Patients with a history of non-cardioembolic stroke or TIA	N=7,648 Duration varied	Primary: Incidence of nonfatal stroke Secondary: Composite of stroke, MI or vascular death, subset analysis comparing outcomes with IR and ER dipyridamole	Primary: Dipyridamole plus aspirin significantly reduced the risk of nonfatal ischemic and hemorrhagic stroke compared to aspirin alone (RR, 0.77; 95% CI, 0.67 to 0.89). Secondary: Dipyridamole plus aspirin significantly reduced the risk of the composite of stroke, MI or vascular death (RR, 0.85; 95% CI, 0.76 to 0.94). Based on four trials, IR dipyridamole plus aspirin did not show a statistically significant reduction in the risk of stroke (RR, 0.83; 95% CI, 0.59 to 1.15) or the composite outcome (RR, 0.95; 95% CI, 0.75 to 1.19) compared to aspirin alone. Based on 2 trials (ESPS 2 and ESPRIT), ER dipyridamole plus aspirin showed a significant reduction in risk for stroke (RR, 0.76; 95% CI, 0.65 to 0.89) and for the composite outcome (RR, 0.82; 95% CI, 0.73 to 0.92) compared to aspirin alone.
Geeganage et al.[34] (2012) Dual therapy with clopidogrel or dipyridamole plus aspirin	MA (12 RCTs) Patients with acute ischemic stroke or TIA	N=3,766 Duration varied	Primary: Recurrent stroke Secondary: Composite of stroke, TIA, ACS and death; composite of	Primary: Dual antiplatelet therapy was associated with a significant decrease in stroke recurrence in comparison to monotherapy (3.3 vs 5.0%; RR, 0.67; 95% CI, 0.49 to 0.93). Secondary: Compared to monotherapy, dual antiplatelet therapy was associated with a significant reduction in the risk of composite endpoint of stroke, TIA,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs monotherapy with aspirin, clopidogrel or dipyridamole			nonfatal stroke, nonfatal MI and vascular death; MI, severe stroke, intracerebral hemorrhage, major bleeding, all-cause death and vascular death	ACS and death (1.7 vs 9.1%; RR, 0.71; 95% CI, 0.56 to 0.91) as well as the composite endpoint of nonfatal stroke, nonfatal MI and vascular death (4.4 vs 6.0%; RR, 0.75; 95% CI, 0.56 to 0.99). No significant differences were seen between dual therapy and monotherapy with regard to the occurrence of MI (RR, 0.71; 95% CI, 0.25 to 2.03), severe stroke (RR, 1.01; 95% CI, 0.91 to 1.12), intracerebral hemorrhage (RR, 1.39; 95% CI, 0.22 to 8.75), all-cause death (RR, 1.34; 95% CI, 0.76 to 2.34) and vascular death (RR, 1.31; 95% CI, 0.59 to 2.93). Major bleeding occurred more frequently with dual therapy compared to monotherapy, though this increase was not statistically significant (RR, 2.09; 95% CI, 0.86 to 5.06).
Sacco et al.[35] (2008) PROFESS Aspirin 25 mg and dipyridamole ER 200 mg BID vs clopidogrel 75 mg QD	DB, RCT Patients ≥55 years of age with a recent ischemic stroke within 90 days of randomization	N=20,332 2.5 years	Primary: Recurrent stroke of any type Secondary: Composite of stroke, MI, or death from vascular causes	Primary: Of those in the aspirin/dipyridamole group, 916 patients (9%) experienced a recurrent stroke compared to 898 patients (8.8%) in the clopidogrel group (HR, 1.01; 95% CI, 0.92 to 1.11). Secondary: Each group had 1,333 patients (13.1%) experience MI or death from a vascular cause (HR, 0.99; 95% CI, 0.92 to 1.07).
Bath et al.[36] (2018) TARDIS Intervention group: aspirin (300 mg load then 50 to 150 mg daily, typically 75 mg), clopidogrel (300 mg load then 75 mg daily), and dipyridamole (200	Blinded-endpoint, MC, OL, RCT Patients ≥50 years of age at risk of a recurrent ischemic stroke and had either a non-cardioembolic ischemic stroke with limb weakness, dysphasia, or neuroimaging-	N=3,096 90 days	Primary: Incidence and severity (scale of 0 to 6, 0 being no symptoms and 6 being death) of recurrent stroke and TIA Secondary: Hemorrhage	Primary: The trial was stopped early on the recommendation of the data monitoring committee. The incidence and severity of recurrent stroke or TIA did not differ between intensive and guideline therapy (6% participants vs 7%; adjusted common OR, 0.90; 95% CI, 0.67 to 1.20; P=0.47). Secondary: The distribution of risk and severity of hemorrhage (using the ordinal scale of fatal, major, moderate, mild, or no hemorrhage) was shifted to more bleeding and bleeding of greater severity in participants randomly assigned to intensive antiplatelet therapy (adjusted common OR, 2.54; 95% CI, 2.05 to 3.16; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg twice daily modified release, given orally, or 100 mg three or four times daily) vs guideline group: either combined aspirin and dipyridamole, or clopidogrel alone (using same doses as above) Randomly assigned antiplatelet drugs were given for 30 days after which participants were treated according to local guidelines, typically with clopidogrel alone or combined aspirin and dipyridamole	positive hemianopia, or a non-cardioembolic TIA with at least 10 min of limb weakness or isolated dysphasia			
Markus et al.[37] (2005) CARESS Clopidogrel 300 mg on day 1, followed by 75 mg QD on days 2 to7 plus aspirin 75 mg QD	DB, PC, RCT Patients with ≥50% carotid stenosis	N=107 7 days	Primary: Proportion of patients who were MES positive on day seven Secondary: Proportion of patients who were MES positive on	Primary: ITT analysis revealed a significant reduction in the primary end point: 43.8% of dual-therapy patients were MES positive on day seven, as compared to 72.7% of monotherapy patients (RR reduction, 39.8%; 95% CI, 13.8 to 58.0; P=0.0046). Secondary: MES frequency per hour was reduced compared to baseline by 61.4% (95% CI, 31.6 to 78.2; P=0.0013) in the dual-therapy group at day seven and by 61.6% (95% CI, 34.9 to 77.4; P=0.0005) on day two.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 75 mg QD			day two, rate of embolization on both days two and seven and their percent change from baseline, safety	There were four recurrent strokes and seven TIAs in the monotherapy group vs no stroke and four TIAs in the dual-therapy group that were considered treatment emergent and ipsilateral to the qualifying carotid stenosis. MES frequency was greater in the 17 patients with recurrent ipsilateral events compared to the 90 without (P=0.0003).
Johnston et al.[38] (2018) POINT Clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin (at a dose of 50 to 325 mg per day) vs aspirin (at a dose of 50 to 325 mg per day) alone	MC, RCT Patients ≥18 years of age with minor ischemic stroke or high-risk TIA	N=4,881 90 days	Primary: Composite of ischemic stroke, MI, or death from ischemic vascular causes Primary safety: Risk of major hemorrhage, which was defined as symptomatic intracranial hemorrhage, intraocular bleeding causing vision loss, transfusion of ≥2 units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death due to hemorrhage	The trial was halted after 84% of the anticipated number of patients had been enrolled because the data and safety monitoring board had determined that the combination of clopidogrel and aspirin was associated with both a lower risk of major ischemic events and a higher risk of major hemorrhage than aspirin alone at 90 days. Primary: The composite primary efficacy outcome occurred in 5.0% of patients receiving clopidogrel plus aspirin and in 6.5% of patients receiving aspirin alone (HR, 0.75; 95% CI, 0.59 to 0.95; P=0.02). Primary safety: The primary safety outcome of major hemorrhage occurred in 0.9% of patients receiving clopidogrel plus aspirin and in 0.4% of patients receiving aspirin alone (HR, 2.32; 95% CI, 1.10 to 4.87; P=0.02). Secondary: The secondary outcome of ischemic stroke occurred in 4.6% of patients receiving clopidogrel plus aspirin and in 6.3% of patients receiving aspirin alone (HR, 0.72; 95% CI, 0.56 to 0.92; P=0.01). Except for stroke, there were no significant differences between treatment groups in the other components of the composite primary efficacy outcome. The risk of total ischemic or hemorrhagic stroke was lower with clopidogrel plus aspirin than with aspirin alone (HR, 0.74; 95% CI, 0.58 to 0.94; P=0.01). In analyses of secondary safety outcomes, there were no significant differences between groups in the rates of hemorrhagic stroke, symptomatic intracerebral hemorrhage, or other symptomatic intracranial hemorrhage considered separately. Death from hemorrhagic vascular

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Each component of the primary efficacy outcome, a composite of the primary efficacy outcome and major hemorrhage, and the total number of ischemic and hemorrhagic strokes	causes occurred in three patients receiving clopidogrel plus aspirin and in two patients receiving aspirin alone (0.1% in each group). Nonfatal, non-intracranial hemorrhage accounted for most of the major hemorrhages. Minor hemorrhage occurred in 1.6% of patients receiving clopidogrel plus aspirin and in 0.5% of patients receiving aspirin alone (HR, 3.12; 95% CI, 1.67 to 5.83; P=0.002).
Wang et al.[39] (2015) CHANCE Clopidogrel-aspirin therapy (loading dose of 300 mg of clopidogrel on day one, followed by 75 mg of clopidogrel per day for 90 days, plus 75 mg of aspirin per day for the first 21 days) vs aspirin-alone group (75 mg/d for 90 days)	DB, PC, RCT Patients ≥40 years of age within 24 hours after onset of minor stroke or high-risk transient ischemic attack	N=5,170 1 year	Primary: Stroke event (ischemic or hemorrhagic) during 1-year follow-up Secondary: A new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), analyzed as a composite outcome and also as individual outcomes	Primary: Throughout the trial, stroke occurred in 275 patients (10.6%) in the clopidogrel-aspirin group, in comparison with 362 patients (14.0%) in the aspirin group (HR, 0.78; 95% CI, 0.65 to 0.93; P=0.006). Beyond month three, 63 (2.7%) of 2346 patients in the clopidogrel-aspirin group and 59 (2.6%) of 2260 patients in the aspirin group had a stroke (HR, 0.96; 95% CI, 0.68 to 1.35; P=0.81). Secondary: The clopidogrel-aspirin group had lower rates of combined secondary vascular events (HR, 0.78; 95% CI, 0.65 to 0.93; P=0.005) and ischemic stroke (HR, 0.77; 95% CI, 0.64 to 0.93; P=0.006) in comparison with the aspirin group. No significant difference was detected between the two groups for other secondary end points. Moderate-to-severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel-aspirin group and in nine patients (0.4%) in the aspirin group (P=0.44).
Johnston et al.[40] (2016) SOCRATES Ticagrelor (180 mg	DB, DD, MC, RCT Patients with a nonsevere ischemic stroke or high-risk	N=13,199 90 days	Primary: Time to the occurrence of stroke, myocardial infarction, or death	Primary: A primary composite end-point event occurred in 442 of the 6589 patients (6.7%) in the ticagrelor group and in 497 of the 6610 patients (7.5%) in the aspirin group (HR, 0.89; 95% CI, 0.78 to 1.01; P=0.07).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
loading dose on day one followed by 90 mg twice daily for days two through 90) vs aspirin (300 mg on day one followed by 100 mg daily for days two through 90).	transient ischemic attack who had not received intravenous or intraarterial thrombolysis and were not considered to have had a cardioembolic stroke who underwent randomization within 24 hours after symptom onset		within 90 days Secondary: Time to ischemic stroke	Secondary: On the basis of the hierarchical testing plan, all analyses of secondary end points were therefore considered to be exploratory and were not used to make conclusions regarding significance. The main secondary end point, ischemic stroke, occurred in 385 patients (5.8%) in the ticagrelor group and 441 patients (6.7%) in the aspirin group (HR, 0.87; 95% CI, 0.76 to 1.00; nominal P=0.046).
Fukuuchi et al.[41] (2008) Ticlopidine 200 mg QD vs clopidogrel 75 mg QD	DB, DD, MC, RCT Japanese patients between the ages of 20 and 80 years who experienced a non-cardioembolic cerebral infarction ≥8 days prior to enrollment	N=1,151 52 weeks	Primary: Safety with emphasis on hematologic changes, hepatic dysfunction, nontraumatic hemorrhage and other serious adverse reactions Secondary: Combined incidence of nonfatal or fatal cerebral infarction or MI, or death due to other vascular causes	Primary: During the 52-week study period, 15.1% of ticlopidine patients and 7.0% of clopidogrel patients had at least one primary safety end point (P<0.001). Significant differences were primarily noted between ticlopidine and clopidogrel for hematologic disorders (2.4 vs 1.0%; P=0.043) and hepatic dysfunction (11.9 vs 4.2%; P<0.001). Study medication was discontinued prematurely due to safety end points in 27 and 17% of patients receiving ticlopidine and clopidogrel, respectively (P<0.001). The HR for the risk of discontinuing study medication due to a primary safety end point was 0.559 (95% CI, 0.434 to 0.721) in favor of clopidogrel. Secondary: The incidence of vascular events did not differ significantly between ticlopidine and clopidogrel (2.6 vs 3.0%, respectively; P=0.948; HR, 0.977; 95% CI, 0.448 to 1.957).
Hass et al.[42] (1989) TASS Ticlopidine 250 mg BID	Blinded, MC, RCT Patients with recent (within three months) minor stroke or TIA	N=3,069 2 to 6 years	Primary: Nonfatal stroke or death Secondary: Adverse events	Primary: Compared to aspirin, ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate was 17% for ticlopidine vs 19% for aspirin; P=0.048). Ticlopidine reduced the risk of stroke after three years by 21% (10% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 650 mg BID				ticlopidine vs 13% for aspirin; P=0.024). Secondary: Ticlopidine significantly increased total cholesterol compared to aspirin (9 vs 2%; P<0.01). Serious gastrointestinal adverse effects were 2.5 times more common in the aspirin group but bleeding from other anatomic sites was infrequent and about equal in the two treatment groups. Severe neutropenia occurred in 0.9% of patients.
Gorelick et al.[43] (2003) AAASPS Ticlopidine 250 mg BID vs aspirin 325 mg BID	DB, MC, RCT African American men and women who recently had a non-cardioembolic ischemic stroke	N=1,809 Up to 2 years	Primary: Composite of recurrent stroke, MI, or vascular death Secondary: Fatal or nonfatal stroke	Primary: There was no statistically significant difference in the percent of patients reaching the primary outcome of recurrent stroke, MI or vascular death between ticlopidine and aspirin (14.7 vs 12.3%, respectively; P=0.12). Secondary: There was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group (P=0.08). The frequency of laboratory-determined serious neutropenia was 3.4% for ticlopidine vs 2.2% for aspirin (P=0.12).
Combined Cardiovascular and Cerebrovascular Conditions				
Simpson et al.[44] (2011) Aspirin vs no aspirin therapy	MA (17 RCTs and four cohort trials) Trials evaluating the use of aspirin in diabetic patients for primary and/or secondary prevention	N=17,522 Duration varied	Primary All-cause mortality Secondary: Cardiovascular-related mortality, MI, stroke	Primary: Analysis of all-cause mortality was based on 1,172 (15.4%) deaths in 7,592 patients receiving aspirin and 1,520 (18.4%) deaths in 8,269 control patients. The pooled RR (25 trials) was 0.93 (95% CI, 0.81 to 1.07; P=0.31). Stratification according to daily aspirin dose did not reveal a significant dose-response relationship. Secondary: Cardiovascular mortality was reported in 447 (7.7%) of 5,798 of patients receiving aspirin and 599 (9.3%) of 6,456 of control patients. The pooled RR (16 trials) was 0.98 (95% CI, 0.76 to 1.25; P=0.86). An MI occurred in 547 (8.3%) of 6,605 patients receiving aspirin and 720 (10.0%) of control patients. The pooled RR (18 trials) was 0.84 (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.65 to 1.09; P=0.20). A stroke occurred in 344 (5.0%) of 6,902 patients receiving aspirin and 418 (5.6%) of 7,420 control patients. The pooled RR (21 trials) was 0.89 (95% CI, 0.892 to 1.16; P=0.80).
Antithrombotic Trialists' Collaboration.[45] (2002) Antiplatelet agents vs control vs one antiplatelet regimen vs another	MA (287 trials) Patients at high risk of occlusive vascular events	N=135,640 Duration varied	Primary: "Serious vascular event" (nonfatal MI, nonfatal stroke or vascular death) Secondary: Not reported	Primary: Overall, antiplatelet therapy reduced the combined outcome of any serious vascular event by 25%, nonfatal MI by 34%, nonfatal stroke by 25%, and vascular mortality by 15% with no apparent adverse effect on other deaths. Aspirin was the most widely studied antiplatelet drug and low dose (75 to 150 mg daily) was at least as effective as higher daily doses for long-term use. In acute settings an initial loading dose of at least 150 mg aspirin may be required. Clopidogrel reduced serious vascular event by 10% compared to aspirin, which was similar to the 12% reduction observed with ticlopidine. The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared to aspirin alone. Secondary: Not reported
Sudlow et al.[46] (2009) Aspirin (325 mg/day for most studies) vs clopidogrel (75 mg QD for most studies) or ticlopidine (250 mg	MA (10 trials) Patients at high risk for serious vascular events, including those with a previous TIA or ischemic stroke	N=26,865 Duration varied	Primary: Composite outcome of stroke, MI, or death from a vascular cause Secondary: Outcomes of adverse drug events	Primary: Treatment with clopidogrel or ticlopidine produced a modest reduction in the odds of a serious vascular event (11.6%) vs aspirin (12.5%; OR, 0.92; 95% CI, 0.85 to 0.99). This corresponds to the avoidance of 10 serious vascular events per 1,000 patients treated with clopidogrel or ticlopidine rather than aspirin for an average of about two years. Secondary: Compared to aspirin, clopidogrel and ticlopidine significantly reduced gastrointestinal adverse effects. However, clopidogrel and ticlopidine increased the odds of skin rash and diarrhea, *ticlopidine* more than clopidogrel. Allocation to *ticlopidine*, but not clopidogrel, significantly increased the odds of neutropenia.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for most studies)				
CAPRIE Steering Committee[47] (1996) CAPRIE Clopidogrel 75 mg QD vs aspirin 325 QD	DB, MC, PG, RCT Patients with recent ischemic stroke (within six months with at least a week of residual neurological signs), recent MI (within 35 days) or symptomatic peripheral arterial disease	N=19,185 1 to 3 years	Primary: Composite outcome of ischemic stroke, MI or vascular death Secondary: Primary outcome and amputation, vascular death, all-cause mortality, safety	Primary: Intention–to-treat analysis showed that patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, MI, or vascular death compared to 5.83% with aspirin, for a RR reduction of 8.7% (95% CI, 0.3 to 16.5; P=0.043) in favor of clopidogrel. Corresponding on-treatment analysis yielded a RR reduction of 9.4% in favor of clopidogrel. For the 6,431 patients admitted to the study with prior stroke, the RR reduction for ischemic stroke, MI, or vascular death was 7.3% in favor of clopidogrel (P=0.26), and the RR reduction for the end point of stroke was 8.0% (P=0.28). For the 6,302 patients admitted to the study with myocardial infarction, an RR increase of 3.7% was associated with clopidogrel (P=0.66). For the 6,452 patients admitted to the study with peripheral arterial disease, an RR of 23.8% was noted in favor of clopidogrel (P=0.0028). Secondary: Clopidogrel reduced the risk of the primary outcome plus amputation by 7.6% compared to aspirin (P=0.076). There was no significant difference between clopidogrel and aspirin with regards to vascular death (1.90 vs 2.06%; P=0.29) and all-cause mortality (3.05 vs 3.11%; P=0.71). There were no major differences in terms of safety. Severe rash (P=0.017) and severe diarrhea (P=0.080) were reported more frequently with clopidogrel and severe upper gastrointestinal discomfort (P=0.096), intracranial hemorrhage (P=0.23) and gastrointestinal hemorrhage (P=0.05) were reported more frequently with aspirin.
Zhou et al.[48] (2012) Aspirin plus clopidogrel	MA, SR (7 RCTs) Trials evaluating the use of aspirin and/or clopidogrel patients	N=48,248 Duration varied	Primary: Major cardiovascular events	Primary: Overall, with combination therapy the harm of major cardiovascular events was significantly reduced by 9% (RR, 0.91; 95% CI, 0.83 to 0.98) compared to monotherapy with aspirin and clopidogrel (six trials; n=46,132).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin vs clopidogrel	for primary and/or secondary prevention		Secondary: Not reported	Combination therapy resulted in a significant 14% reduction in the harm of MI compared to monotherapy with aspirin and clopidogrel (RR, 0.86; 95% CI, 0.76 to 0.97) (seven trials; n=48,248). Combination therapy resulted in a significant 16% reduction in the harm of stroke compared to monotherapy with aspirin and clopidogrel (RR, 0.84; 95% CI, 0.72 to 0.99) (seven trials; n=48,248). There was no evidence to show that combination therapy could reduce the risk of mortality, regardless of total mortality, vascular death, or non-vascular death compared to monotherapy aspirin and clopidogrel. There was no effect of combination therapy on the harm of revascularization events compared to monotherapy with aspirin and clopidogrel. Combination therapy significantly increased the harm of major bleeding events by 62% compared to monotherapy with aspirin and clopidogrel (RR, 1.62; 95% CI, 1.26 to 2.08) (seven trials; n=46,073). Secondary: Not reported
DeSchryver et al.[49] (2007) Dipyridamole with or without other antiplatelet drugs vs control (no drug or another antiplatelet drug)	MA (29 trials) Patients with arterial vascular disease (angina, CAD, MI, nephropathy, PAD, retinopathy, stroke and TIA)	N=23,019 Duration varied	Primary: Secondary prevention of vascular death and vascular events (defined as vascular death or any death from an unknown cause, nonfatal stroke or nonfatal MI) Secondary: Not reported	Primary: Compared to control, dipyridamole had no clear effect on vascular death (RR, 0.99; 95% CI, 0.87 to 1.12). The dose of dipyridamole or type of presenting vascular disease did not influence this result. Compared to control, dipyridamole appeared to reduce the risk of vascular events (RR, 0.88; 95% CI, 0.81 to 0.95). This effect was only statistically significant in patients presenting with cerebral ischemia. There was no evidence that dipyridamole alone was more efficacious than aspirin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Conditions (Acute Coronary Syndrome, Heart Failure, Myocardial Infarction, Angina Pectoris)				
Armstrong et al.[50] (2020) VICTORIA Vericiguat 10 mg once daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with chronic heart failure, reduced left ventricular ejection fraction <45%, and elevated natriuretic peptide levels	N=5,050 12 months	Primary: Composite of death from CV causes or first hospitalization from heart failure Secondary: Components of primary outcome, subsequent hospitalizations for heart failure, death of any cause	Primary: Death from cardiovascular causes or first hospitalization for heart failure occurred in 897 patients (35.5%) in the vericiguat group and in 972 patients (38.5%) in the placebo group (HR, 0.90; 95% CI, 0.82 to 0.98; P=0.02). Secondary: Death from cardiovascular causes occurred in 414 patients (16.4%) in the vericiguat group and in 441 patients (17.5%) in the placebo group HR, 0.93; 95% CI, 0.81 to 1.06). Hospitalization for heart failure occurred in 691 patients (27.4%) in the vericiguat group and in 747 patients (29.6%) in the placebo group (HR, 0.90; 95% CI, 0.81 to 1.00). There were 1223 total hospitalizations (first and recurrent events) for heart failure (38.3 events per 100 patient-years) in the vericiguat group and 1336 total hospitalizations (42.4 events per 100 patient-years) in the placebo group (HR, 0.91; 95% CI, 0.84 to 0.99; P=0.02). Death from any cause occurred in 512 patients (20.3%) in the vericiguat group and in 534 patients (21.2%) in the placebo group (HR, 0.95; 95% CI, 0.84 to 1.07; P=0.38).
CURE Trial Investigators[51] (2001) CURE Clopidogrel (300 mg immediately, followed by 75 mg QD) plus aspirin vs aspirin	DB, PC, RCT Patients with NSTEMI, presenting within 24 hours of symptom onset	N=12,562 3 to 12 months	Primary: Composite of death from cardiovascular causes, nonfatal MI, or stroke (first primary outcome); composite of the first primary outcome or refractory ischemia (second primary outcome)	Primary: A composite of death from cardiovascular causes, nonfatal MI, or stroke occurred in 9.3% of patients in the clopidogrel and aspirin group compared to 11.4% of patients in the aspirin group (RR, 0.80; 95% CI, 0.72 to 0.90; P<0.001). When refractory ischemia was included with the first primary outcome, the composite rate was 16.5% in the clopidogrel and aspirin group compared to 18.8% for aspirin alone (RR, 0.86; 95% CI, 0.79 to 0.94; P<0.001). Secondary: Significant reductions in nonfatal MI (5.2 vs 6.7%) and trends toward

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Severe ischemia, heart failure, need for revascularization, safety	reduction in death (5.1 vs 5.5%) and stroke (1.2 vs 1.4%) with clopidogrel plus aspirin vs aspirin alone were noted. The percentages of patients with in hospital refractory or severe ischemia, recurrent angina, heart failure and revascularization procedures were also significantly lower with clopidogrel plus aspirin vs aspirin alone (P<0.05 for all). There were significantly more patients with major bleeding in the clopidogrel plus aspirin group than in the aspirin group (3.7 vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; P=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.1 vs 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56; P=0.13).
COMMIT Collaborative Group[52] (2005) COMMIT Clopidogrel 75 mg/day plus aspirin 162 mg/day vs aspirin 162 mg/day	MC, PC, RCT Patients admitted to the hospital within 24 hours of suspected acute MI, mean age 61 years	N=45,852 15 days (mean duration)	Primary: Composite of death, reinfarction or stroke; death from any cause Secondary: Safety	Primary: Allocation to clopidogrel plus aspirin produced a highly significant 9% proportional reduction in death, reinfarction or stroke compared to aspirin alone (actual reductions 9.2 vs 10.1%, respectively; P=0.002), corresponding to nine fewer events per 1,000 patients treated for about two weeks. There was also a significant 7% proportional reduction in any death in the clopidogrel plus aspirin group compared to aspirin alone (7.5 vs 8.1%; P=0.03). Secondary: Considering all fatal, transfused, or cerebral bleeds together, no significant excess risk was noted with clopidogrel plus aspirin vs aspirin alone, either overall (0.58 vs 0.55%, respectively; P=0.59) or in patients older than 70 years or in those given fibrinolytic therapy.
Sabatine et al.[53] (2005) CLARITY-TIMI 28 Clopidogrel 300 mg loading dose, followed by 75 mg QD plus aspirin	DB, MC, PC, RCT Patients 18 to 75 years of age who presented within 12 hours after the onset of a STEMI	N=3,491 30 days	Primary: Composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography (death	Primary: The primary end point was reached in 15.0% of patients receiving clopidogrel vs 21.7% for placebo, representing an absolute reduction of 6.7% in the rate and 36% in the odds of reaching the end point with clopidogrel therapy (95% CI, 27 to 47; P<0.001). By 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin Patients received a fibrinolytic agent, and heparin when appropriate.			or recurrent MI by day 8 or hospital discharge in patients who did not undergo angiography) Secondary: Safety	or recurrent ischemia leading to the need for urgent revascularization by 20% (from 14.1 to 11.6%; P=0.03). Secondary: The rates of major bleeding and intracranial hemorrhage were similar in the two groups.
Peripheral Artery Disease				
Berger et al.[54] (2009) Aspirin vs aspirin/ dipyridamole vs placebo	MA (18 trials) Patients with PAD	N=5,269 Duration varied	Primary: Relative risk reduction of aspirin therapy on the composite end point of nonfatal MI, nonfatal stroke, and cardiovascular death Secondary: All-cause mortality and each component of the primary end point	Primary: There was no overall statistically significant difference in the composite outcome of nonfatal MI, nonfatal stroke and cardiovascular death between the aspirin and placebo or control groups (18 RCTs: RR, 0.88; 95% CI, 0.76 to 1.04) There was a significantly lower incidence of nonfatal stroke in the aspirin groups (18 RCTs: RR, 0.66; 95% CI, 0.47 to 0.94). Secondary: There were no statistically significant differences between the groups for any other secondary efficacy outcome. There was no statistically significant difference between the groups in incidence of major bleeding, but this was not formally assessed in many included RCTs.

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice-daily, ER=extended-release, IR=immediate-release, QD=once-daily
Study abbreviations: AC=active-controlled, CS=cross sectional, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OB=observational, OL=open-label, PA=parallel arm, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=cross over trial
Miscellaneous abbreviations: ACS=acute coronary syndrome, BARC= Bleeding Academic Research Consortium, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, CT=computerized tomography, CV=cardiovascular, FEV_1=forced expiratory volume in one second, GFR=glomerular filtration rate, GP IIb/IIIa inhibitor=glycoprotein IIb/IIIa inhibitor, GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries, HR=hazard ratio, INR=International Normalized Ratio, IRR=incidence rate ratio, ITT=intention to treat, IU=international units, MES=microembolic signal, MI=myocardial infarction, MRI=magnetic resonance imaging, NSTE ACS=non-ST-segment elevation acute coronary syndromes, NSTEMI=non-ST-segment elevation myocardial infarction, OR=odds ratio, PAD=peripheral arterial disease, PCI=percutaneous coronary intervention, PPI=proton pump inhibitor, RR=relative risk, STEMI=ST-segment elevation myocardial infarction, TIA=transient ischemic attack, TIMI=thrombolysis in myocardial infarction, TRACER=Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome, TRA2P-TIMI 50=Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction

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 Vasodilating Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Dipyridamole	injection, tablet	N/A	N/A	$$$
Vericiguat	tablet	Verquvo®	$$$$$	N/A
Combination Products				
Aspirin and dipyridamole	extended-release capsule	N/A	N/A	$$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The vasodilating agents, miscellaneous play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes (ACS), myocardial infarction (MI), stroke, and transient ischemic attack (TIA).[1-7,13] Dipyridamole, , and aspirin-dipyridamole are available generically.

Aspirin has been the most frequently studied antiplatelet agent and is usually the reference drug to which other treatments are compared.[45] Aspirin is the antiplatelet agent recommended as first-line in most treatment guidelines for general use. Aspirin is recommended as a first-line option for the initial management of noncardioembolic stroke or TIA, ACS, and MI, as well as for primary and secondary prevention in patients with cerebrovascular, cardiovascular, and peripheral vascular diseases. Low-dose aspirin (75 to 150 mg/day) is an effective platelet-aggregation inhibitor regimen for long-term use, but in acute settings, an initial loading dose of ≥150 mg may be required. Other platelet inhibitors are usually reserved for patients with contraindications or severe intolerance to aspirin or who have failed aspirin monotherapy or in high-risk patients when dual antiplatelet therapy is recommended. Dual antiplatelet therapy with aspirin plus clopidogrel, prasugrel, or ticagrelor is recommended for patients with ACS (non ST-segment elevation myocardial infarction [NSTEMI] and unstable angina). Antiplatelet therapy is also recommended in patients with ST-segment elevation myocardial infarction (STEMI). For patients with noncardioembolic ischemic strokes or TIAs, fixed-dose aspirin and dipyridamole is suggested instead of aspirin alone, and clopidogrel may be considered instead of aspirin alone to reduce the risk of recurrent stroke and other cardiovascular events.[5-14] For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination product has been studied in patients who have had an event while receiving aspirin.[8]

Dipyridamole has been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease compared to placebo, but has not been shown to be more effective than aspirin.[28,29] Aspirin plus dipyridamole significantly reduced the risk of stroke by 37% compared to 18% with aspirin and 16% with dipyridamole. There was no significant difference in all cause mortality among the active treatment groups.[28] Aspirin plus dipyridamole significantly reduced the composite of death, nonfatal stroke or MI and major bleeding to 13% of patients compared to 16% for aspirin monotherapy; however, the combination regimen was discontinued more often, mainly because of headache.[31]

Vericiguat is indicated to reduce the risk of cardiovascular death and heart failure hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics in adults with symptomatic chronic heart failure and ejection fraction <45%. FDA approval of vericiguat was based on the VICTORIA study. It was a randomized, double-blind, multicenter, placebo-controlled trial evaluating efficacy of vericiguat in addition to standard therapy in 5,050 patients who had chronic heart failure and an ejection fraction <45%. Patients were randomized to vericiguat 10 mg or placebo. The primary outcome was a composite of death from cardiovascular causes or first hospitalization due to heart failure. Secondary endpoints included subsequent hospitalizations for heart failure and death of any cause. The composite primary endpoint occurred in 37.5% of those taking vericiguat compared to 38.5% of those taking placebo, a statistically significant difference. Subsequent hospitalizations for heart failure occurred in 27.4% of patients taking vericiguat compared to 29.6% taking placebo, a statistically significant difference. There was no statistically significant difference in death from any cause between the two groups.[50] Common side effects include hypotension and anemia.[3]

There is insufficient evidence to support that one brand vasodilating agents, miscellaneous 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 vasodilating agents, miscellaneous 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 vasodilating agents, 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiarrhythmic Agents
AHFS Class 240404
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I. Overview

Cardiac contractions are regulated by electrical activity in the heart originating in the sinoatrial node and propagated through ion channels, chiefly sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) channels. Arrhythmias are caused by abnormalities in formation and transmission of impulses and are classified based on their origin: supraventricular (atrial or atrioventricular junction) or ventricular.[1]

There is extensive data regarding the cellular mechanisms by which some of the antiarrhythmic drugs exert their action; however, the general approach to antiarrhythmic therapy remains largely empirical.[2] The antiarrhythmic agents are generally grouped into specific categories or classes based on their predominant mechanisms: (1) sodium channel blockade, (2) blockade of sympathetic autonomic effects in the heart, (3) prolongation of the effective refractory period, and (4) calcium channel blockade.[1] E. M. Vaughan Williams proposed the first antiarrhythmic classification system in 1970 and it is now the most widely used scheme. The Vaughan Williams classification system divides the antiarrhythmic agents into the following classes: Class I: fast sodium channel blockers, Class II: β-blockers, Class III: repolarization potassium current blockers, and Class IV: calcium channel antagonists.[2] The agents included in this review differ with regards to their Food and Drug Administration-approved indications, mechanism of action, pharmacokinetic properties, drug interactions, and adverse events.

The antiarrhythmic agents that are included in this review, as well as their Vaughan Williams Classifications, are listed in Table 1. This review encompasses all dosage forms and strengths. All of the antiarrhythmic agents are available in a generic formulation, with the exception of dronedarone. This class was last reviewed in February 2022.

Table 1. Antiarrhythmic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Vaughan Williams Classification	Current PDL Agent(s)
Amiodarone	injection, tablet	Nexterone®, Pacerone®*	III	amiodarone
Disopyramide	capsule, extended-release capsule	Norpace®*, Norpace CR®	IA	disopyramide
Dofetilide	capsule	Tikosyn®*	III	dofetilide
Dronedarone	tablet	Multaq®	I, II, III, IV	none
Flecainide	tablet	N/A	IC	flecainide
Mexiletine	capsule	N/A	IB	mexiletine
Propafenone	extended-release capsule, tablet	Rythmol SR®*	IC	propafenone
Quinidine	extended-release tablet, tablet	N/A	IA	quinidine

*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 treatment guidelines that incorporate the use of the antiarrhythmic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antiarrhythmic Agents

Clinical Guideline	Recommendation (s)

American Heart Association/American College of Cardiology/ Heart Rhythm Society: **2019 Focused Update of the 2014 Guideline for the Management of Patients with Atrial Fibrillation (2019)**[3]	<u>Recommendations for selecting an anticoagulant regimen</u>
	• For patients with atrial fibrillation (AF) and an elevated CHA_2DS_2-VASc score of two or greater in men or three or greater in women, oral anticoagulants are recommended. Options include:
	  o Warfarin
	  o Dabigatran
	  o Rivaroxaban
	  o Apixaban
	  o Edoxaban
	• Non–vitamin K oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve)
	• Among patients treated with warfarin, the international normalized ratio (INR) should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable.
	• In patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), the CHA_2DS_2-VASc score is recommended for assessment of stroke risk.
	• For patients with AF who have mechanical heart valves, warfarin is recommended.
	• Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.
	• Renal function and hepatic function should be evaluated before initiation of a NOAC and should be reevaluated at least annually.
	• In patients with AF, anticoagulant therapy should be individualized on the basis of shared decision-making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient's values and preferences.
	• For patients with atrial flutter, anticoagulant therapy is recommended according to the same risk profile used for AF.
	• Reevaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risks.
	• For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended.
	• For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy.
	• For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.
	• For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD (serum creatinine ≥1.5 mg/dL [apixaban], CrCl 15 to 30 mL/min [dabigatran], CrCl <50 mL/min [rivaroxaban], or CrCl 15 to 50 mL/min [edoxaban]) with an elevated CHA_2DS_2-VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, apixaban, or edoxaban).

Clinical Guideline	Recommendation (s)
	• For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered. • In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk. • The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve. <u>Interruption and bridging anticoagulation</u> • Bridging therapy with unfractionated heparin or low-molecular-weight heparin is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding. • For patients with AF without mechanical heart valves who require interruption of warfarin for procedures, decisions about bridging therapy (unfractionated heparin or low-molecular-weight heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated. • Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure. • Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding. <u>Rhythm control: recommendations for prevention of thromboembolism</u> • For patients with AF or atrial flutter of 48 hours' duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0), a factor Xa inhibitor, or direct thrombin inhibitor is recommended for at least three weeks before and at least four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score or the method (electrical or pharmacological) used to restore sinus rhythm. • For patients with AF or atrial flutter of more than 48 hours' duration or unknown duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated. • After cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile and bleeding risk profile. • For patients with AF or atrial flutter of less than 48 hours' duration with a CHA_2DS_2-VASc score of 2 or greater in men and 3 or greater in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor is reasonable as soon as possible before cardioversion, followed by long-term anticoagulation therapy. • For patients with AF or atrial flutter of 48 hours' duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform transesophageal echocardiography before cardioversion and proceed with cardioversion if no left atrial thrombus is identified, including in the LAA, provided that anticoagulation is achieved before transesophageal echocardiography and maintained after cardioversion for at least four weeks. • For patients with AF or atrial flutter of less than 48 hours' duration with a CHA_2DS_2-VASc score of 0 in men or 1 in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor, versus no anticoagulant therapy, may be considered before cardioversion, without the need for

Clinical Guideline	Recommendation (s)
	postcardioversion oral anticoagulation. Recommendations for AF complicating acute coronary syndrome (ACS) • For patients with ACS and AF at increased risk of systemic thromboembolism (based on CHA_2DS_2-VASc risk score of 2 or greater), anticoagulation is recommended unless the bleeding risk exceeds the expected benefit. • Urgent direct-current cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control. • Intravenous beta blockers are recommended to slow a rapid ventricular response to AF in patients with ACS who do not display HF, hemodynamic instability, or bronchospasm. • If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone percutaneous coronary intervention (PCI) with stenting for ACS, it is reasonable to choose clopidogrel in preference to prasugrel. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist is reasonable to reduce the risk of bleeding as compared with triple therapy. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with $P2Y_{12}$ inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily is reasonable to reduce the risk of bleeding as compared with triple therapy. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with triple therapy. • If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF who are at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) and who have undergone PCI with stenting (drug eluting or bare metal) for ACS, a transition to double therapy (oral anticoagulant and $P2Y_{12}$ inhibitor) at four to six weeks may be considered. • Administration of amiodarone or digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability. • Administration of nondihydropyridine calcium antagonists may be considered to slow a rapid ventricular response in patients with ACS and AF only in the absence of significant HF or hemodynamic instability.
American Heart Association/American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation (2014)[4]**	Recommendations for risk-based antithrombotic therapy: Class I • In patients with atrial fibrillation (AF), antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences (Level of Evidence: C). • Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent (Level of Evidence: B). • In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence: B). • For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) should be

Clinical Guideline	Recommendation (s)
	based on type and location of the prosthesis (Level of Evidence: B). • For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran, rivaroxaban, or apixaban (Level of Evidence: B). • For patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (Level of Evidence: A) • For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor is recommended (Level of Evidence: C). • Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks (Level of Evidence: C). • Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding (Level of Evidence: C). • For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated (Level of Evidence: C). • Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (Level of Evidence: B). • For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF (Level of Evidence: C). Class IIa • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Level of Evidence: B). • For patients with nonvalvular AF with a CHA_2DS_2-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (Level of Evidence: B). Class IIb • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence: C). • For patients with nonvalvular AF and moderate-to-severe chronic kidney disease with a CHA_2DS_2-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established (Level of Evidence: C). • In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture (Level of Evidence: C). • Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B). Class III: No Benefit • The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical

Clinical Guideline	Recommendation (s)
	trials regarding the balance of risks and benefits (Level of Evidence: C). Class III: Harm • The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (Level of Evidence: B). <u>Recommendations for rate control:</u> Class I • Control of the ventricular rate using a beta blocker or nondihydropyridine (non-DHP) calcium channel blocker (CCB) is recommended for patients with paroxysmal, persistent, or permanent AF (Level of Evidence: B). • Intravenous administration of a beta blocker or non-DHP CCB is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Level of Evidence: B). • In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range (Level of Evidence: C). Class IIa • A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF (Level of Evidence: B). • Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (Level of Evidence: B). • Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (Level of Evidence: B). Class IIb • A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and left ventricular systolic function is preserved (Level of Evidence: B). • Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated (Level of Evidence: C). Class III: Harm • AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications (Level of Evidence: C). • Non-DHP CCBs should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise (Level of Evidence: C). • In patients with pre-excitation and AF, digoxin, non-DHP CCBs, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation. (Level of Evidence: B). • Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death (Level of Evidence: B). <u>Recommendations for thromboembolism prevention</u>: Class I • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method used to restore sinus rhythm (Level of Evidence: B). • For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation

Clinical Guideline	Recommendation (s)
	should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated (Level of Evidence: C). • For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy (Level of Evidence: C). • Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile (Level of Evidence: C). Class IIa • For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks (Level of Evidence: B). • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion (Level of Evidence: C). Class IIb • For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation (Level of Evidence: C). <u>Recommendations for pharmacological cardioversion</u> Class I • Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Level of Evidence: A). Class IIa • Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF (Level of Evidence: A). • Propafenone or flecainide ("pill-in-the-pocket") in addition to a beta blocker or non-DHP CCB is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (Level of Evidence: B). Class III: Harm • Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes (Level of Evidence: B). <u>Recommendations for antiarrhythmic drugs to maintain sinus rhythm</u> Class I • Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended (Level of Evidence: C). • The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Level of Evidence: A): o Amiodarone o Dofetilide o Dronedarone o Flecainide

Clinical Guideline	Recommendation (s)
	○ Propafenone ○ Sotalol • The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug (Level of Evidence: C). • Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated (Level of Evidence: C). Class IIa • A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy (Level of Evidence: C). Class IIb • It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF (Level of Evidence: C). Class III: Harm • Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent (Level of Evidence: C), including dronedarone (Level of Evidence: B). • Dronedarone should not be used for treatment of AF in patients with New York Heart Association class III and IV HF or patients who have had an episode of decompensated HF in the past four weeks. (Level of Evidence: B). <u>Upstream therapy</u> Class IIa • An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF with reduced left ventricular ejection fraction (Level of Evidence: B). Class IIb • Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (Level of Evidence: B). • Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (Level of Evidence: A). Class III: No Benefit • Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (Level of Evidence: B).
National Institute for Health and Clinical Excellence: **Dronedarone for the Treatment of Non-permanent Atrial Fibrillation (2010)[5]** (last modified Dec 2012)	• Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent atrial fibrillation (AF): ○ Whose AF is not controlled by first-line therapy (usually including β-blockers), that is, as a second-line treatment option and after alternative options have been considered AND ○ Who have at least one of the following cardiovascular risk factors: ▪ Hypertension requiring drugs of at least two different classes. ▪ Diabetes mellitus. ▪ Previous transient ischemic attack, stroke, or systemic embolism. ▪ Left atrial diameter of 50 mm or greater, OR ▪ Age ≥70 years. ○ And in patients who do not have left ventricular systolic dysfunction AND who do not have a history of, or current, heart failure. • Patients who do not meet the above criteria who are currently receiving dronedarone should have the option to continue treatment until they and their

Clinical Guideline	Recommendation (s)
	clinicians consider it appropriate to stop.
American College of Cardiology/American Heart Association/ Heart Rhythm Society: **Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2017)[6]**	<u>Medication therapy for treatment or prevention of ventricular arrhythmias (VA)</u> • In patients with heart failure with reduced ejection fraction, treatment with a beta blocker, a mineralocorticoid receptor antagonist, and either an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, or an angiotensin receptor-neprilysin inhibitor is recommended to reduce sudden cardiac death (SCD) and all-cause mortality. • With the exception of beta blockers (e.g., metoprolol succinate, carvedilol), there is no evidence from randomized controlled trials that antiarrhythmic medications for VA improve survival when given for the primary or secondary prevention of SCD. • Except in specific circumstances, sodium channel blockers (Vaughn-Williams class I agents) have a limited role in the prevention of VT/SCD; this is based on a lack of survival benefit and increased mortality observed during chronic therapy in patients with ischemic heart disease. • Because of their excellent safety profile and effectiveness in treating VA and reducing the risk of SCD, beta blockers are often first-line antiarrhythmic therapy. • Amiodarone's overall long-term effect on survival is controversial, with most studies showing no clear advantage over placebo. A few studies and a meta-analysis of several large studies have shown a reduction in SCD using amiodarone in patients with LV dysfunction due to prior myocardial infarction and non-ischemic cardiomyopathy, but the SCD-HeFT trial showed no survival benefit from amiodarone compared with placebo. • Although sotalol has some efficacy in suppressing VA, it has significant proarrhythmic effects and has not been shown to improve survival. • For the treatment of most VA, nondihydropyridines calcium channel blockers have no role.
American Association for Thoracic Surgery: **2014 AATS Guidelines for the Prevention and Management of Peri-Operative Atrial Fibrillation and Flutter (POAF) for Thoracic Surgical Procedures (2014)[7]**	<u>Recommended prevention strategies for all postoperative atrial fibrillation (POAF) patients</u> • Patients taking β-blockers prior to thoracic surgery should continue them in the postoperative period to avoid β-blockade withdrawal. • Intravenous magnesium supplementation may be considered to prevent postoperative AF when serum magnesium level is low or it is suspected that total body magnesium is depleted. • Digoxin should not be used for prophylaxis against AF. <u>Recommended prevention strategies for intermediate to high-risk POAF patients</u> • It is reasonable to administer diltiazem to those patients with preserved cardiac function who are not taking β-blockers preoperatively in order to prevent POAF. • It is reasonable to consider the postoperative administration of amiodarone to reduce the incidence of POAF for intermediate and high risk patients undergoing pulmonary resection. • Postoperative administration of intravenous amiodarone may be considered to prevent POAF in patients undergoing esophagectomy. • Atorvastatin may be considered to prevent POAF for statin naïve patients scheduled for intermediate and high risk thoracic surgical procedures. <u>Rate control recommendations for patients with new onset POAF</u> • Intravenous administration of beta-blockers (e.g., esmolol or metoprolol) or nondihydropyridine calcium channel blockers (diltiazem or verapamil) is recommended to achieve rate control (heart rate ≤110 bpm) for patients who develop POAF with rapid ventricular response. • Caution should be used with patients with hypotension, left ventricular (LV)

Clinical Guideline	Recommendation (s)
	dysfunction, or heart failure. • Combination use of atrioventricular (AV) nodal blocking agents, such as beta-blockers (e.g., esmolol or metoprolol), nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, can be useful to control heart rates when a single agent fails to control rates of POAF. The choice should be individualized and doses modified to avoid bradycardia. • For patients with hypotension, heart failure or LV dysfunction, or when other measures are unsuccessful or contraindicated, intravenous amiodarone can be useful for control of heart rate. Amiodarone could result in conversion to sinus rhythm, and if it is initiated after 48 hours of AF, both a transesophageal echocardiography (TEE) when possible, to rule out left atrial/LA appendage (LA/LAA) thrombus, and full anticoagulation should be considered. • For patients with heart failure, LV dysfunction or hypotension, intravenous digoxin may be considered for rate control of POAF. • For patients with ventricular preexcitation (i.e., Wolff-Parkinson-White syndrome) and POAF, use of AV nodal blocking agents, such as beta-blockers (e.g., esmolol or metoprolol), intravenous amiodarone, nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, should be avoided. <u>Recommendations for the use of antiarrhythmic drugs for pharmacologic cardioversion of POAF</u> • Restoration of sinus rhythm with pharmacologic cardioversion is reasonable in patients with symptomatic, hemodynamically stable POAF. Intravenous amiodarone can be useful for pharmacologic cardioversion of POAF. • It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm for patients with recurrent or refractory POAF. • Amiodarone, sotalol, flecainide, propafenone, or dofetilide can be useful to maintain sinus rhythm in patients with POAF, depending on underlying heart disease, renal status and other comorbidities. • Flecainide or propafenone may be considered for pharmacologic cardioversion of POAF and maintenance of sinus rhythm if the patient has had no prior history of myocardial infarction, coronary artery disease, impaired LV function, significant LV hypertrophy, or valvular heart disease that is considered moderate or greater. These agents may need to be combined with an AV nodal blocking agent. • Intravenous ibutilide or procainamide may be considered for pharmacologic conversion of POAF for patients with structural heart disease and new onset POAF, but no hypotension or manifestations of congestive heart failure. Serum electrolytes and QTc interval must be within a normal range and patients must be closely monitored during and for at least six hours after the infusion if either ibutilide or procainamide. • Intravenous ibutilide or procainamide may be considered for patients with POAF and an accessory pathway. • Flecainide and propafenone should not be used to treat POAF in patients with a history of a prior myocardial infarction, coronary artery disease, and/or severe structural heart disease, including severe left ventricular hypertrophy, or significantly reduced left ventricular ejection fraction. • Dronedarone should not be used for treatment of POAF in patients with heart failure. <u>Recommendations for prevention of thromboembolism for patients with stable atrial fibrillation/flutter undergoing direct current cardioversion</u> • For stable patients with POAF of 48-hours duration or longer, anticoagulation (with warfarin for INR 2.0 to 3.0, a novel oral anti-coagulant [NOAC] or

Clinical Guideline	Recommendation (s)
	LMWH) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the method (electrical or pharmacological) used to restore sinus rhythm. • During the first 48 hours after the onset of POAF, the need for anticoagulation before and after direct current (DC) cardioversion may be based on the patient's risk of thromboembolism (CHA_2DS_2-VASc score) balanced by the risk of postoperative bleeding. • For POAF lasting longer than 48 hours, as an alternative to three weeks of therapeutic anticoagulation prior to cardioversion of POAF, it is reasonable to perform TEE in search of thrombus in the LA or LA appendage, preferably with full anticoagulation at the time of TEE in anticipation of DC cardioversion after the TEE. • For POAF lasting longer than 48 hours in patients who are not candidates for TEE (e.g., post-esophageal surgery), an initial rate control strategy combined with therapeutic anticoagulation using warfarin (aiming for INR 2.0 to 3.0), a direct thrombin inhibitor (e.g. dabigatran), factor Xa inhibitor (e.g. rivaroxaban, apixaban), or LMWH is recommended for at least three weeks prior to and four weeks after cardioversion. • Anticoagulation recommendations for cardioversion of atrial flutter are similar to those for atrial fibrillation. • For patients with an identified thrombus, cardioversion should not be performed until a longer period of anticoagulation is achieved (usually at least three weeks) and in accordance with established AF guidelines. <u>Management of anticoagulation for new onset POAF</u> • For the prevention of strokes for patients who develop POAF lasting longer than 48 hours, it is recommended to administer antithrombotic medications similarly to non-surgical patients. Anticoagulation within the first 48-hours of POAF should be considered based on the CHA_2DS_2-VASc risk score of the patient for stroke weighed against the risk of postoperative bleeding. • New oral anticoagulants (dabigatran, rivaroxaban, apixaban) are reasonable as an alternative to warfarin for patients who do not have a prosthetic heart valve, hemodynamically significant valve disease, and/or severe renal impairment or risk of GI bleeding. • It is reasonable to continue anticoagulation therapy for four weeks after the return of sinus rhythm because of the possibility of slowly resolving impairment of atrial contraction with an associated ongoing risk for thrombus formation and for delayed embolic events. • New oral anticoagulants should be avoided for patients at risk for serious bleeding (including GI bleeding) as they cannot be readily reversed. However, their use may be recommended in situations where achievement of a therapeutic INR with warfarin has proved to be difficult.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antiarrhythmic agents 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 Antiarrhythmic Agents[8-15]

Indication	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Atrial Arrhythmias								
Chronic therapy in patients at high risk of symptomatic atrial fibrillation (AF)/flutter								✔ *
Conversion of AF and atrial flutter to normal sinus rhythm			✔					
Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter) in patients with AF/atrial flutter of greater than one week duration who have been converted to normal sinus rhythm			✔ †					
Prevention of paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms and paroxysmal supraventricular tachycardias (PSVT) associated with disabling symptoms in patients without structural heart disease					✔			
Prolong the time to recurrence of symptomatic AF in patients without structural heart disease							✔ ‡	
Prolong the time to recurrence of PAF and PSVT associated with disabling symptoms in patients without structural heart disease							✔ §	
Reduce the risk of hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF				✔				

Indication	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Restore normal sinus rhythm in patients with symptomatic AF/atrial flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response								✔
Ventricular Arrhythmias								
Initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy	✔ (Nexterone®)‖							
Prevention of life-threatening ventricular arrhythmias (e.g., sustained VT)					✔			
Suppression of recurrent life-threatening ventricular arrhythmias (e.g., sustained VT)								✔
Treatment of life-threatening ventricular arrhythmias (e.g., sustained VT)		✔				✔	✔ §	
Treatment of recurrent VF	✔ ¶ (Cordarone®, Pacerone®)							
Treatment of recurrent hemodynamically unstable VT	✔ ¶ (Cordarone®, Pacerone®)							
Miscellaneous								
Treatment of life-threatening *Plasmodium falciparum* malaria								✔

*This includes patients who have had previous episodes of atrial fibrillation/flutter that were so frequent and poorly tolerated as to outweigh, in the judgment of the physician and the patient, the risks of prophylactic therapy with quinidine sulfate. The increased risk of death should specifically be considered. Quinidine sulfate should be used only after alternative measures (e.g., use of other drugs to control the ventricular rate) have been found to be inadequate.

†Because dofetilide can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic.

‡Sustained-release formulation.

§Immediate-release formulation.

‖ Nexterone® can also be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medications. During or after treatment with Nexterone®, patients may be transferred to oral amiodarone therapy. Use Nexterone® for acute treatment until patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48 to 96 hours, but Nexterone® may be safely administered for longer periods if necessary.

¶ Because of its life-threatening side effects and the substantial management difficulties associated with its use, amiodarone is indicated only for the treatment of the life-threatening recurrent ventricular arrhythmias when these have not responded to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated.

IV. Pharmacokinetics

The pharmacokinetic parameters of the antiarrhythmic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antiarrhythmic Agents[16]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Amiodarone	35 to 65	96	Liver (% not reported; extensive)	Renal (<1) Bile (% not reported; primary)	26 to 107 days
Disopyramide	80	50 to 65	Liver (45)	Renal (40 to 80) Feces (15)	4 to 10 hours
Dofetilide	>90	60 to 70	Liver (50)	Renal (80) Feces (<10)	7.5 to 10 hours
Dronedarone	15	>98	Liver (% not reported; extensive)	Renal (6) Feces 84)	13 to 19 hours
Flecainide	70 to 95	40	Liver (% not reported; extensive)	Renal (81 to 90) Feces (4 to 6)	7 to 22 hours
Mexiletine	80 to 90	50 to 70	Liver (% not reported; extensive)	Renal (8 to 15)	6 to 17 hours
Propafenone	12	85 to 97	Liver (% not reported; extensive)	Renal (<1) Feces (53)	5 to 8 hours
Quinidine	70 to 80 (oral)	80 to 90	Liver (50 to 90)	Renal (5 to 20) Feces (1 to 3)	6 to 8 hours

V. Drug Interactions

Major drug interactions with the antiarrhythmic agents are listed in Table 5.

Table 5. Major Drug Interactions with the Antiarrhythmic Agents[16]

Generic Name(s)	Interaction	Mechanism
Amiodarone, Disopyramide, Flecainide, Propafenone, Quinidine	Cisapride	Possible additive prolongation of the QT interval, increasing the risk of life-threatening cardiac arrhythmias.
Amiodarone, Disopyramide, Dofetilide, Flecainide, Propafenone, Quinidine	Dronedarone	Possible additive or synergistic prolongation of the QT interval, increasing the risk of life-threatening cardiac arrhythmias.
Amiodarone, Disopyramide, Dofetilide, Dronedarone, Quinidine	Macrolide and related antibiotics	An additive or synergistic increase in the QT interval may result, increasing the risk of life-threatening cardiac arrhythmias.
Amiodarone, Disopyramide, Dofetilide, Dronedarone,	Phenothiazines	Concurrent use may lead to the prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.

Generic Name(s)	Interaction	Mechanism
Quinidine		
Amiodarone, Disopyramide, Dofetilide, Quinidine	Quinolones	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Amiodarone, Disopyramide, Dofetilide, Quinidine	Ziprasidone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility with concurrent administration.
Amiodarone, Mexiletine, Quinidine	Hydantoins	Phenytoin may increase the hepatic metabolism of certain antiarrhythmics via stimulation of microsomal enzymes.
Amiodarone, Dronedarone	Protease inhibitors	Protease inhibitors may inhibit the metabolism (CYP3A4) of certain antiarrhythmics, thereby increasing antiarrhythmic concentrations and increasing the risk of toxicity.
Amiodarone, Disopyramide	Vardenafil	Mechanism of interaction is unknown. The risk of life-threatening cardiac arrhythmias may be increased with concurrent use.
Dofetilide, Quinidine	Azole antifungals	Certain azole antifungal agents may inhibit the metabolism (CYP3A4) and active renal secretion of dofetilide or quinidine. Plasma dofetilide or quinidine concentrations may be elevated, increasing the risk of serious cardiovascular events.
Disopyramide, Quinidine	Hydantoins	Phenytoin appears to increased hepatic metabolism of disopyramide via stimulation of microsomal enzymes.
Propafenone, Quinidine	Rifamycins	Rifamycins may induce the hepatic microsomal enzymes responsible for metabolizing certain antiarrhythmics, whose increased clearance may lead to a decrease in plasma levels and a possible loss of therapeutic effects.
Amiodarone	Digoxin	Amiodarone may increase the oral bioavailability and decrease the systemic clearance of digoxin; additional mechanisms may exist. Mechanism of interaction is unknown but it is thought that multiple mechanisms are involved.
Amiodarone	Fentanyl	Mechanism of interaction is unknown. Profound bradycardia, sinus arrest, and hypotension have occurred with concurrent administration.
Amiodarone	HMG-CoA reductase inhibitors	Amiodarone may inhibit the metabolism of HMG-CoA reductase inhibitors (cytochrome P450 [CYP] 3A4) thereby increasing plasma concentrations and increasing the risk of toxicity.
Amiodarone	Quinidine	Mechanism of interaction is unknown. Concurrent therapy may lead to an increase in quinidine concentrations and produce potentially fatal cardiac dysrhythmias.
Amiodarone	Warfarin	Amiodarone inhibits the metabolism (CYP1A2 and CYP2C9) of the R- and S-enantiomers of warfarin; therefore the hypoprothrombinemic effects may be augmented.
Amiodarone	Cyclosporine	Mechanism of the interaction is unknown. Amiodarone may inhibit the metabolism of cyclosporine which may lead to an increase in cyclosporine blood concentrations, possibly increasing the risk of nephrotoxicity.
Amiodarone	Flecainide	Amiodarone may decrease the metabolism of flecainide and plasma levels may be increased.
Amiodarone	Procainamide	Mechanism of the interaction is unknown. Amiodarone may increase serum concentrations of procainamide.
Disopyramide	Rifampin	Hepatic metabolism of disopyramide is increased with concurrent use.
Dofetilide	Cimetidine	Cimetidine may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide

Generic Name(s)	Interaction	Mechanism
		elimination. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	Megestrol	Concurrent use results in inhibition of the renal cation transport system responsible for dofetilide elimination, increasing the risk of ventricular arrhythmias.
Dofetilide	Thiazide diuretics	Thiazide diuretics may increase potassium excretion causing hypokalemia which may increase the risk of torsades de pointes.
Dofetilide	Trimethoprim	Trimethoprim may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	Verapamil	Verapamil may increase the rate of dofetilide absorption by increasing portal blood flow thereby increasing dofetilide plasma concentrations which may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dronedarone	Azole antifungal agents	Dronedarone plasma concentrations may be elevated, increasing the risk of toxicity, including life-threatening cardiotoxicity.
Dronedarone	Cyclosporine	Dronedarone plasma concentrations may be elevated, increasing the risk of toxicity, including life-threatening cardiotoxicity.
Dronedarone	Nefazodone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by nefazodone. Inhibition of CYP3A by nefazodone may decrease the metabolic elimination of dronedarone.
Dronedarone	Tricyclic antidepressants	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Dronedarone	Digoxin	Plasma concentrations and pharmacologic effects of digoxin may be increased, due to inhibition of P-glycoprotein efflux transport.
Flecainide	Amiodarone	Flecainide plasma levels may be increased.
Flecainide	Ritonavir	Large increases in serum flecainide concentrations may occur, increasing the risk of flecainide toxicity.
Mexiletine	Propafenone	Mexiletine plasma concentrations may be elevated in extensive metabolizers, increasing the risk of side effects.
Mexiletine	Theophylline	Mexiletine may impair hepatic elimination and increase plasma concentrations of theophylline. Additive arrhythmogenic effects may also occur.
Mexiletine	Tizanidine	Tizanidine plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Propafenone	Digoxin	Mechanism of interaction is unknown. Serum digoxin levels may be increased, resulting in toxicity.
Propafenone	Ritonavir	Large increases in serum propafenone concentrations may occur, increasing the risk of propafenone toxicity.
Propafenone	β-blockers	The pharmacologic effects of beta-blockers metabolized by the liver may be increased.
Propafenone	Quinidine	Serum propafenone levels may be increased in rapid, extensive metabolizers of the drug (≈ 90% of the patients), increasing the pharmacologic effects of propafenone.
Propafenone	Serotonin reuptake inhibitors	Propafenone plasma concentrations may be increased by serotonin-norepinephrine reuptake inhibitors, due to inhibition of cytochrome CYP2D6 isoenzymes.
Quinidine	Digoxin	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.
Quinidine	Mifepristone	Quinidine plasma concentrations may be elevated due to inhibition of metabolism by mifepristone, increasing the pharmacologic effects and risk of adverse reactions
Quinidine	Protease	Protease inhibitors may inhibit the metabolism (CYP3A4) of

Generic Name(s)	Interaction	Mechanism
	inhibitors	quinidine. Large increases in serum quinidine concentrations may occur, increasing the risk of quinidine toxicity.
Quinidine	Verapamil	Verapamil may decrease the clearance of quinidine and prolong its half-life which may lead to hypotension, bradycardia, ventricular tachycardia and atrioventricular block.
Quinidine	Warfarin	Quinine derivatives also may inhibit the hepatically synthesized clotting factors. Anticoagulation may be potentiated by quinine derivatives and hemorrhage may occur.
Quinidine	Antacids	Certain antacids may increase serum quinidine concentrations, which may result in toxicity.
Quinidine	Anti-cholinesterases	Quinidine derivatives may reverse the effects of anticholinesterases and vice versa.
Quinidine	Aripiprazole	Quinidine may inhibit the hepatic metabolism (CYP2D6) of aripiprazole thereby increasing plasma concentrations and potentiating the pharmacologic effects and adverse reactions.
Quinidine	Barbiturates	Barbiturates may increase the metabolic clearance of quinidine thereby decreasing quinidine serum concentrations and elimination half-life.
Quinidine	β-blockers	Quinidine may inhibit the oxidative metabolism of certain beta-blockers. The effects of certain β-blockers may be increased in "extensive metabolizers."
Quinidine	Cimetidine	Inhibition of hepatic microsomal enzymes by cimetidine may decrease the metabolic elimination of quinidine. Additional mechanisms may exist including a decrease in renal clearance of quinidine possibly due to competition with cimetidine for renal tubular secretion.
Quinidine	Codeine	Quinidine may decrease pharmacologic effects of codeine, due to inhibition of CYP2D6 isoenzymes and thereby decreased metabolic conversion of codeine to morphine. Loss of analgesic effect may occur.
Quinidine	Diltiazem	The therapeutic and adverse effects of quinidine may be increased due to inhibition of the hepatic metabolism of quinidine by competition for the same isozyme.
Quinidine	Nifedipine	Plasma concentrations and pharmacologic effects of quinidine may be decreased by nifedipine. Plasma concentrations and pharmacologic effects of nifedipine may be increased by quinidine, which may decrease the first-pass metabolism of nifedipine by inhibiting aromatization.
Quinidine	Non-depolarizing muscle relaxants	Concurrent use of these agents may cause synergistic pharmacologic effects. Non-depolarizing muscle relaxants effects may be enhanced by quinine and quinine derivatives.
Quinidine	Succinylcholine	Quinidine may produce a decrease in plasma cholinesterase activity resulting in a slowed metabolic rate for succinylcholine. The neuromuscular blockade produced by succinylcholine may be prolonged.

VI. Adverse Drug Events

The most common adverse drug events reported with the antiarrhythmic agents are listed in Table 6. The boxed warnings for the antiarrhythmic agents are listed in Tables 7 through 14.

Table 6. Adverse Drug Events (%) Reported with the Antiarrhythmic Agents[8-15]

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Cardiovascular								
Alters pacing threshold	-	-	-	-	<1	-	-	-
Angina	-	-	-	-	<1	2	2 to 5	6
Arrhythmia	1 to 10	-	-	-	-	-	-	1 to 10
Asystole	1 to 10	-	-	-	-	-	-	-
Atrial fibrillation	-	-	-	-	-	-	1	-
AV block	5	<1	0.4 to 1.5	-	<1	<1	1 to 3	-
AV dissociation	-	-	-	-	-	-	<1	-
Bradycardia	3 to 5	-	-	3	<1	-	1 to 2	<1
Bundle branch block	-	-	<2	-	-	-	0 to 1	-
Cardiac arrest	1 to 10	-	<2	-	-	-	<1	-
Cardiogenic shock	1 to 10	-	-	-	-	<1	-	-
Chest pain	-	1 to 10	10	-	5	3 to 8	1 to 2	-
Conduction abnormalities	1 to 10	1 to 10	-	-	-	-	0 to 1	-
Congestive heart failure	-	1 to 10	-	-	-	-	-	-
Edema	1 to 10	1 to 10	-	✔	3.5	-	0 to 1	-
Electromechanical dissociation	1 to 10	-	-	-	-	-	-	-
Heart block	-	-	<2	-	<1	-	-	<1
Hypertension	-	-	-	-	-	-	0 to 1	-
Hypotension	<1	1 to 10	-	-	-	<1	-	✔
Myocardial infarction	-	-	<2	-	-	-	-	-
Palpitations	-	-	-	-	6	4 to 8	1 to 3	7
Premature ventricular contractions	-	-	-	-	-	1 to 2	1 to 2	-
Proarrhythmia	<1	<1	-	-	4 to 12	10 to 15	2 to 10	-
P-R increased	-	-	-	-	<1	-	-	-
QRS duration	-	-	-	-	<1	-	1 to 2	-
QT interval increased	<1	-	-	-	-	-	-	>10
QTc prolonged	-	-	-	28	-	-	-	-
SA node dysfunction	1 to 3	-	-	-	-	-	-	-
Sinus arrest	<1	-	-	-	-	<1	-	-
Sinus node dysfunction	-	-	-	-	1.2	-	<1	-
Stroke	-	-	<2	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Tachycardia	-	-	-	-	1 to 3	-	-	<1
Torsades de pointes	<1	-	0.9 to 10.5	-	-	<1	-	<1
Ventricular arrhythmia	-	-	-	-	<1	-	-	-
Ventricular fibrillation	<1	-	0 to 0.4	-	-	-	-	<1
Ventricular rate increase	-	-	-	-	<1	-	-	<1
Ventricular tachycardia	1 to 10	-	2.6 to 3.7	-	-	-	1 to 3	<1
Central Nervous System								
Abnormal gait/ataxia	3 to 40	-	-	-	-	-	-	-
Amnesia	-	-	-	-	<1	-	<1	-
Anxiety	-	-	-	-	1 to 3	-	1 to 2	-
Ataxia	-	-	-	-	1 to 3	10 to 20	0 to 2	-
Cerebral hypoperfusion	-	-	-	-	-	-	-	<1
Coma	-	-	-	-	-	-	<1	-
Confusion	<1	-	-	-	-	1 to 10	<1	<1
Delirium	-	-	-	-	-	-	-	<1
Depersonalization	-	-	-	-	<1	-	-	-
Depression	-	<1	-	-	1 to 3	2	<1	<1
Disorientation	<1	-	-	-	-	-	-	-
Dizziness	3 to 40	1 to 10	8	-	19 to 30	20 to 25	4 to 15	-
Drowsiness	-	-	-	-	-	-	1	-
Encephalopathy	<1	-	-	-	-	-	-	-
Euphoria	-	-	-	-	<1	-	-	-
Fatigue	3 to 40	1 to 10	-	-	8	-	2 to 6	7
Fever	-	-	-	-	1 to 3	-	-	<1
Flushing	-	-	-	-	-	-	-	<1
Hallucinations	<1	-	-	-	-	<1	-	<1
Headache	3 to 40	1 to 10	11	-	4 to 10	1 to 10	2 to 5	7
Impaired memory	3 to 40	-	-	-	-	-	-	-
Insomnia	3 to 40	<1	4	-	1 to 3	5 to 7	0 to 2	-
Involuntary movement	3 to 40	-	-	-	-	-	-	-
Lightheadedness	-	-	-	-	-	11 to 25	-	15
Malaise	3 to 40	1 to 10	-	-	1 to 3	-	-	-
Memory loss	-	-	-	-	-	-	<1	-
Nervousness	-	1 to 10	-	-	5	5 to 10	-	2
Paresis	-	-	-	-	1 to 3	-	-	-
Peripheral neuropathy	3 to 40	-	-	-	-	-	-	-
Poor coordination	3 to 40	-	-	-	-	10	-	1

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Psychotic reaction/psychosis	-	<1	-	-	-	<1	<1	<1
Seizure	-	-	-	-	-	<1	0.3	-
Sleep disturbances	3 to 40	-	-	-	-	-	-	3
Somnolence	-	-	-	-	1 to 3	-	-	-
Syncope	-	1 to 10	<2	-	1 to 10	<1	1 to 2	1 to 8
Tardive dyskinesia	-	-	-	-	<1	-	-	-
Vertigo	-	-	-	-	1 to 3	-	<1	<1
Visual disturbances	<10	-	-	-	16	-	-	<1
Dermatological								
Abnormal pigmentation	-	-	-	-	-	-	-	<1
Allergic dermatitis	-	-	-	≤5	-	-	-	-
Alopecia	<1	-	-	-	<1	<1	<1	-
Eczematous dermatitis	-	-	-	≤5	-	-	-	<1
Epididymitis	<1	-	-	-	-	-	-	-
Erythema multiforme	<1	-	-	-	-	-	-	-
Exfoliative dermatitis	<1	-	-	-	<1	<1	-	<1
Flushing	1 to 10	-	-	-	-	-	-	-
Generalized dermatoses	-	1 to 10	-	-	-	-	-	-
Leukocytoclastic vasculitis	<1	-	-	-	-	-	-	-
Lichen planus	-	-	-	-	-	-	-	<1
Livedo reticularis	-	-	-	-	-	-	-	<1
Melanin pigmentation of hard palate	-	-	-	-	-	-	-	<1
Phlebitis	1 to 10	-	-	-	-	-	-	-
Photophobia	<1	-	-	-	<1	-	-	-
Photosensitivity	10 to 75	-	-	<1	-	-	-	<1
Pruritus	<1	1 to 10	-	≤5	<1	-	<1	<1
Purpura	-	-	-	-	-	-	<1	-
Rash	<1	1 to 10	3	≤5	1 to 3	4	1 to 3	5
Slate blue skin discoloration	<10	-	-	-	-	-	-	-
Spontaneous ecchymosis	<1	-	-	-	-	-	-	-
Stevens-Johnson syndrome	<1	-	-	-	-	<1	-	-
Toxic cutaneous blisters	-	<1	-	-	-	-	-	-
Toxic epidermal necrolysis	<1	-	-	-	-	-	-	-
Urticaria	-	-	-	-	<1	<1	-	<1
Vasculitis	<1	-	-	-	-	-	-	-
Endocrine and Metabolic								
Decreased libido	1 to 10	-	-	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Erectile dysfunction	<1	-	-	-	-	-	-	-
Gynecomastia	-	<1	-	-	-	-	-	-
Hyperthyroidism	3 to 10	-	-	-	-	-	-	-
Hypothyroidism	1 to 22	-	-	-	-	-	-	-
Impotence	<1	1 to 3	-	-	-	<1	<1	-
Gastrointestinal								
Abdominal bloating	-	1 to 10	-	-	-	-	-	-
Abdominal distention	-	1 to 10	-	-	-	-	-	-
Abdominal pain	1 to 10	-	3	4	3	1	1 to 2	-
Abnormal salivation	1 to 10	-	-	-	-	-	-	-
Abnormal taste	1 to 10	-	-	-	<1	-	3 to 23	>10
Angioedema	<1	-	<2	-	-	-	-	<1
Anorexia	10 to 33	1 to 10	-	-	1 to 3	-	1 to 2	>10
Cholestasis	-	-	-	-	-	-	0.1	-
Constipation	10 to 33	11	-	-	1	4 to 5	2 to 7	-
Diarrhea	-	1 to 10	3	9	0.7 to 3.0	4 to 5	1 to 3	35
Dry throat	-	1 to 10	-	-	-	-	-	-
Dysgeusia	-	-	-	<1	-	-	-	-
Dyspepsia	-	-	-	2	-	-	1 to 3	-
Dysphagia	-	-	-	-	-	<1	-	-
Esophagitis	-	-	-	-	-	-	-	<1
Flatulence	-	1 to 10	-	-	-	-	0 to 1	-
Gastrointestinal distress	-	-	-	-	-	41	-	>10
Nausea	10 to 33	1 to 10	5	5	9	40	2 to 11	>10
Stomach cramping	-	-	-	-	-	-	-	22
Swollen lips/tongue/mouth	-	-	-	-	<1	-	-	-
Upper gastrointestinal bleeding	-	-	-	-	-	<1	-	-
Vomiting	10 to 33	1 to 10	-	2	-	40	2 to 11	>10
Weight gain	-	1 to 10	-	-	-	-	-	-
Xerostomia	-	32	-	-	-	3	1 to 2	-
Genitourinary								
Urinary frequency	-	1 to 10	-	-	-	-	-	-
Urinary hesitancy	-	14 to 23	-	-	-	-	-	-
Urinary retention	-	1 to 10	-	-	<1	<1	-	-
Urinary urgency	-	1 to 10	-	-	-	-	-	-
Hematological								
Agranulocytosis	<1	<1	-	-	-	<1	<1	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Aplastic anemia	<1	-	-	-	-	-	-	-
Coagulation abnormalities	1 to 10	-	-	-	-	-	-	-
Granulocytopenia	-	-	-	-	<1	-	<1	-
Hemolytic anemia	<1	-	-	-	-	-	-	<1
Hemoptysis	<1	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	<1	<1	<1	-
Neutropenia	<1	-	-	-	-	-	-	-
Pancytopenia	<1	-	-	-	-	-	-	<1
Thrombocytopenia	<1	<1	-	-	<1	<1	<1	<1
Hepatic								
AST or ALT level >2x normal	15 to 50	<1	-	-	-	-	-	-
Cirrhosis	<3	-	-	-	-	-	-	-
Hepatic necrosis	-	-	-	-	-	<1	-	-
Hepatitis	<3	-	-	-	-	<1	0.03	<1
Hepatotoxicity	-	<1	<2	-	-	-	-	<1
Laboratory Test Abnormalities								
Hypercholesterolemia	-	1 to 10	-	-	-	-	-	-
Hyperglycemia	<1	-	-	-	-	-	<1	-
Hypertriglyceridemia	<1	1 to 10	-	-	-	-	-	-
Hypoglycemia	-	<1	-	-	-	-	-	-
Hypokalemia	-	1 to 10	-	✔	-	-	-	-
Hypomagnesemia	-	-	-	✔	-	-	-	-
Serum creatinine increased	-	<1	-	51	-	-	-	-
Musculoskeletal								
Arthralgia	-	-	-	-	-	1	0 to 1	<1
Back pain	-	-	3	-	-	-	-	-
Facial paralysis	-	-	<2	-	-	-	-	-
Flaccid paralysis	-	-	<1	-	-	-	-	-
Lupus	-	<1	-	-	-	<1	<1	-
Lupus-like syndrome	-	-	-	-	-	-	-	<1
Muscle pain (myalgia)	-	1 to 10	-	-	-	-	-	<1
Myopathy	<1	-	-	-	-	-	-	-
Neuropathy	-	<1	-	-	<1	2 to 4	<1	-
Paralysis	-	-	<2	-	-	-	-	-
Paresthesia	-	<1	<2	-	1	2	<1	-
Parkinsonian symptoms	<1	-	-	-	-	-	-	-
Rhabdomyolysis	<1	-	-	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Trembling	-	-	-	-	-	>10	-	-
Tremor	3 to 40	-	-	-	5	13	0 to 1	2
Unsteady gait	-	-	-	-	-	>10	-	-
Weakness	<1	1 to 10	-	7	5	5	1 to 2	5
Ocular								
Blurred vision	-	1 to 10	-	-	1 to 10	5 to 7	1 to 6	1 to 10
Corneal micro-deposits	>90	-	-	-	<1	-	-	-
Diplopia	-	-	-	-	1 to 3	-	-	-
Dry eyes	-	1 to 10	-	-	-	-	-	-
Halo vision	<5	-	-	-	-	-	-	-
Mydriasis	-	-	-	-	-	-	-	<1
Nystagmus	-	-	-	-	-	6	-	-
Optic neuritis	1	-	-	-	-	-	-	<1
Optic neuropathy	<1	-	-	-	-	-	-	-
Uveitis	-	-	-	-	-	-	-	<1
Visual disturbances	2 to 9	-	-	-	-	-	-	-
Renal								
Acute renal failure	<1	-	-	-	-	-	<1	-
Nephropathy	-	-	-	-	-	-	-	<1
Nephrotic syndrome	-	-	-	-	-	-	<1	-
Respiratory								
Acute respiratory distress syndrome	2	-	-	-	-	-	-	-
Alveolar pneumonitis	✔	-	-	-	-	-	-	-
Apnea	-	-	-	-	-	-	<1	-
Bronchiolitis obliterans organizing pneumonia	<1	-	-	-	-	-	-	-
Bronchospasm	<1	-	-	-	<1	-	-	<1
Dyspnea	<1	1 to 10	6	-	~10	3	2 to 5	-
Hypersensitivity pneumonitis	✔	-	-	-	-	-	-	-
Pleuritis	<1	-	-	-	-	-	-	-
Pneumonitis	✔	-	-	-	<1	-	-	<1
Pulmonary alveolar hemorrhage	<1	-	-	-	-	-	-	-
Pulmonary edema	<1	-	-	-	-	-	-	-
Pulmonary fibrosis	✔	-	-	-	-	<1	-	-
Pulmonary inflammation	✔	-	-	-	-	-	-	-
Pulmonary mass	<1	-	-	-	-	-	-	-
Pulmonary toxicity	2 to 17	-	-	-	-	-	-	-
Respiratory failure	<1	<1	-	-	-	-	-	<1

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Respiratory tract infection	-	-	7	-	-	-	-	-
Wheezing	<1	-	-	-	-	-	-	1 to 10
Other								
Abnormal smell	1 to 10	-	-	-	-	-	-	-
Anaphylactic shock	<1	-	-	-	-	-	-	-
Blood urea nitrogen increased	-	<1	-	-	-	-	-	-
Bone marrow granuloma	<1	-	-	-	-	-	-	-
Cholestatic jaundice	-	<1	-	-	-	-	-	-
Cinchonism	-	-	-	-	-	-	-	<1
Diaphoresis	-	-	-	-	-	-	1	-
Flu syndrome	-	-	4	-	-	-	-	-
Hearing impairment	-	-	-	-	-	-	-	<1
Hypoxia	<1	-	-	-	-	-	-	-
Increased bleeding time	-	-	-	-	-	-	<1	-
Increased creatine phosphokinase	-	-	-	-	-	-	-	<1
Lymphadenopathy	-	-	-	-	-	-	-	<1
Myelofibrosis	-	-	-	-	-	<1	-	-
Pancreatitis	<1	-	-	-	-	<1	-	-
Pseudotumor cerebri	<1	-	-	-	-	-	-	-
Sicca syndrome	-	-	-	-	-	-	-	<1
Syndrome of inappropriate antidiuretic hormone secretion	<1	-	-	-	-	-	<1	-
Thyroid cancer/nodules	<1	-	-	-	-	-	-	-
Thyrotoxicosis	<1	-	-	-	-	-	-	-
Tinnitus	-	-	-	-	1 to 3	2 to 3	<1	1 to 10
Vascular collapse	-	-	-	-	-	-	-	<1
Vasculitis	-	-	-	-	-	-	-	<1

✓ Percent not specified.
- Event not reported.

Table 7. Boxed Warning for Amiodarone[15]

WARNING
Life-threatening arrhythmias: Amiodarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity. **Pulmonary toxicity:** Amiodarone can cause pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 17% in some series of patients. Pulmonary toxicity has been fatal about 10% of the time. Obtain a baseline chest X-ray and pulmonary function tests, including diffusion capacity, when amiodarone therapy is initiated. Repeat history, physical exam, and chest X-ray every three to six months. **Hepatotoxicity:** Amiodarone can cause hepatotoxicity, which can be fatal. Obtain baseline and periodic liver transaminases and discontinue or reduce dose if the increase exceeds 3 times normal or doubles in a patient with an elevated baseline. Discontinue amiodarone if the patient experiences signs or symptoms of clinical liver injury. **Worsened arrhythmias:** Amiodarone can exacerbate arrhythmias. Initiate amiodarone in a clinical setting where continuous ECGs and cardiac resuscitation are available.

Table 8. Boxed Warning for Disopyramide[15]

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an myocardial infarction more than six days but less than two years previously, an excessive mortality or nonfatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared to that seen in patients assigned to carefully matched placebo-treated groups (3%). The average duration of treatment with encainide or flecainide in this study was 10 months. The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of disopyramide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of disopyramide as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Table 9. Boxed Warning for Dofetilide[15]

WARNING
To minimize the risk of induced arrhythmia, patients initiated or re-initiated on dofetilide should be placed for a minimum of three days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. For detailed instructions regarding dose selection, see Administration and Dosage. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.

Table 10. Boxed Warning for Dronedarone[15]

WARNING
Increased risk of death, stroke, and heart failure: Dronedarone is contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or New York Heart Association class IV heart failure. Dronedarone doubles the risk of death in these patients. Dronedarone is contraindicated in patients in atrial fibrillation (AF) who will not or cannot be cardioverted into normal sinus rhythm. In patients with permanent AF, dronedarone doubles the risk of death, stroke, and hospitalization for heart failure.

Table 11. Boxed Warning for Flecainide[15]

WARNING

Mortality:
Flecainide was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with flecainide compared to that seen in patients assigned to a carefully matched placebo-treated group. This rate was 5.1% for flecainide and 2.3% for the matched placebo. The average duration of treatment with flecainide in this study was 10 months.

The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain, but at present, it is prudent to consider the risks of Class Ic agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

Ventricular proarrhythmic effects in patients with atrial fibrillation/flutter:
A review of the world literature revealed reports of 568 patients treated with oral flecainide for paroxysmal atrial fibrillation/flutter. Ventricular tachycardia was experienced in 0.4% of these patients. Of 19 patients in the literature with chronic atrial fibrillation, 10.5% experienced ventricular tachycardia (VT) or ventricular fibrillation (VF). Flecainide is not recommended for use in patients with CAF. Case reports of ventricular proarrhythmic effects in patients treated with flecainide for atrial fibrillation/flutter have included increased premature ventricular contractions, VT, VF, and death.

As with other Class I agents, patients treated with flecainide for atrial flutter have been reported with 1:1 atrioventricular conduction due to slowing the atrial rate. A paradoxical increase in the ventricular rate also may occur in patients with atrial fibrillation who receive flecainide. Concomitant negative chronotropic therapy such as digoxin or β-blockers may lower the risk of this complication.

Table 12. Boxed Warning for Mexiletine[15]

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non–life-threatening ventricular arrhythmias who had an myocardial infarction (MI) more than six days but less than two years previously, an excessive mortality or nonfatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3%). The average duration of treatment with encainide or flecainide in this study was 10 months. The applicability of the CAST results to other populations (e.g., those without recent MI) is uncertain. Considering the known proarrhythmic properties of mexiletine and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of mexiletine as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias. In postmarketing experience, abnormal liver function tests have been reported, some in the first few weeks of therapy with mexiletine. Most of these have been observed in the setting of congestive heart failure or ischemia and their relationship to mexiletine has not been established.

Table 13. Boxed Warning for Propafenone[15]

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an myocardial infarction more than 6 days but less than 2 years previously, an increased rate of death or reversed cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared to that seen in patients assigned to placebo (3%). The average duration of treatment with encainide or flecainide in this study was 10 months.

WARNING
The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) or other antiarrhythmic drugs is uncertain, but at present, it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be avoided in patients with nonlife-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening symptoms or signs.

Table 14. Boxed Warning for Quinidine[15]

WARNING
In many trials of antiarrhythmic therapy for non–life-threatening arrhythmias, active antiarrhythmic therapy has resulted in increased mortality; the risk of active therapy is probably greatest in patients with structural heart disease. In the case of quinidine used to prevent or defer recurrence of atrial flutter/fibrillation, the best available data come from a meta-analysis. In the patients studied in the analyzed trials, the mortality associated with the use of quinidine was more than 3 times as great as the mortality associated with the use of placebo. Another meta-analysis showed that in patients with various non–life-threatening ventricular arrhythmias, the mortality associated with the use of quinidine was consistently greater than that associated with the use of any of a variety of alternative antiarrhythmics.

VII. Dosing and Administration

The usual dosing regimens for the antiarrhythmic agents are listed in Table 15.

Table 15. Usual Dosing Regimens for the Antiarrhythmic Agents[8-16]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amiodarone	Ventricular arrhythmias: Injection (Nexterone®): initial, 1,000 mg IV over 24 hours; maintenance, 720 mg IV per 24 hours; in the event of breakthrough episodes of ventricular fibrillation or hemodynamically unstable ventricular tachycardia, use 150 mg IV supplemental infusions Injection, tablet: initial, loading dose of 800 to 1,600 mg/day for one to three weeks, followed by 600 to 800 mg/day for one month; maintenance, 400 to 600 mg/day	Safety and efficacy in pediatrics have not been established.	Tablet: 100 mg 200 mg 400 mg Injection: 50 mg/mL 1.5 mg/mL 1.8 mg/mL
Disopyramide	Ventricular arrhythmias: Capsule, extended-release capsule: 400 to 800 mg/day administered in divided doses Capsule (when rapid control of ventricular arrhythmia is essential): initial, loading dose of 200 or 300 mg; maintenance, 400 to 800 mg/day administered in divided doses	Safety and efficacy in pediatrics have not been established.	Capsule: 100 mg 150 mg Extended-release capsule: 100 mg 150 mg
Dofetilide	Atrial arrhythmias: Capsule: 500 µg twice daily; dosage must be individualized according to	Safety and efficacy in pediatrics have not been established.	Capsule: 125 µg 250 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	calculated creatinine clearance and QTc		500 µg
Dronedarone	Atrial arrhythmias: Tablet: 400 mg twice daily	Safety and efficacy in pediatrics have not been established.	Tablet: 400 mg
Flecainide	Atrial arrhythmias: Tablet (prevention of paroxysmal atrial fibrillation/flutter): initial, 50 mg every 12 hours; maintenance, doses may be increased in increments of 50 mg twice daily every four days until efficacy is achieved Ventricular arrhythmias: Tablet (prevention of paroxysmal supraventricular tachycardias): initial, 50 mg every 12 hours; maintenance, doses may be increased in increments of 50 mg twice daily every four days until efficacy is achieved; maximum, 300 mg/day Tablet (prevention of ventricular arrhythmias): initial, 100 mg every 12 hours; maintenance, up to 150 mg every 12 hours; maximum, 400 mg/day	Safety and efficacy in pediatrics have not been established.	Tablet: 50 mg 100 mg 150 mg
Mexiletine	Ventricular arrhythmias: Capsule: initial, loading dose of 400 mg, followed by 200 mg every eight hours OR 200 mg every eight hours; maintenance, 200 to 300 mg given every eight hours; maximum, 1,200 mg/day	Safety and efficacy in pediatrics have not been established.	Capsule: 150 mg 200 mg 250 mg
Propafenone	Atrial arrhythmias: Extended-release capsule: initial, 225 mg every 12 hours; maintenance, 325 to 425 mg every 12 hours Tablet: initial, 150 mg every eight hours; maintenance, 225 to 300 mg every eight hours; maximum, usefulness and safety of doses >900 mg/day have not been established Ventricular arrhythmias: Tablet: initial, 150 mg every eight hour; maintenance, 225 to 300 mg every eight hours; maximum, usefulness and safety of doses >900 mg/day have not been established	Safety and efficacy in pediatrics have not been established.	Extended-release capsule: 225 mg 325 mg 425 mg Tablet: 150 mg 225 mg 300 mg
Quinidine	Atrial arrhythmias: Extended-release tablet: initial, 324 mg every eight to 12 hours; dosage must be individualized according to tolerance and QTc Injection: <5 to 10 mg/kg IV as a total dose; if conversion to sinus rhythm has not been achieved after infusion of 10	Safety and efficacy for the treatment of atrial and ventricular arrhythmias in pediatrics have not been established. *Plasmodium falciparum* malaria:	Extended-release tablet: 324 mg (quinidine gluconate) Injection (quinidine gluconate): 80 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg/kg, then the infusion should be discontinued, and other means of conversion should be considered Tablet: initial, 200 mg every six hours; dosage must be individualized according to tolerance and QTc <u>Ventricular arrhythmias:</u> Injection: <5 to 10 mg/kg IV as a total dose; if conversion to sinus rhythm has not been achieved after infusion of 10 mg/kg, then the infusion should be discontinued, and other means of conversion should be considered <u>*Plasmodium falciparum* malaria:</u> Injection: initial, loading dose of 15 mg/kg; maintenance, 7.5 mg/kg infused over four hours every eight hours for seven days OR initial, loading dose of 6.25 mg/kg; maintenance, 12.5 µg/kg/min Tablet: maintenance, 300 mg every eight hours for seven days OR maintenance, provide approximately as much daily quinine base as the patient had been receiving quinidine base	Injection: initial, loading dose of 6.25 mg/kg; maintenance, 12.5 µg/kg/min Tablet: maintenance, 300 mg every eight hours for seven days OR maintenance, provide approximately as much daily quinine base as the patient had been receiving quinidine base	Tablet (quinidine sulfate): 200 mg 300 mg

IV=intravenous.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antiarrhythmic agents are summarized in Table 16.

Table 16. Comparative Clinical Trials with the Antiarrhythmic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cairns et al.[17] (1997) CAMIAT Amiodarone loading dose of 10 mg/kg in 2 divided doses daily for 2 weeks, followed by 300 to 400 mg/day for 3 to 5 months, then 200 to 300 mg/day for 4 months, and finally 200 mg/day for 5 to 7 days per week for 16 months vs placebo	DB, MC, PC, RCT Patients >19 years who had an acute MI within the previous 6 to 45 days, and the development of new 40 ms Q-waves in ≥2 adjacent ECG leads or the development of a dominant R-wave in V1, 24 hour ambulatory ECG monitoring that recorded a mean of ≥10 VDPs per hour (≥18 hours of monitoring required), or at ≥1 run of VT	N=1,202 2 years	Primary: RVF or AD Secondary: AD, cardiac death, all-cause mortality	Primary: Twenty-five patients receiving amiodarone compared to 39 patients receiving placebo experienced an RVF or AD (RR reduction, 38.2; 95% CI, -2.1 to 62.6; P=0.029). Secondary: Twenty-four patients receiving amiodarone compared to 33 patients receiving placebo experienced an AD (RR reduction, 29.3; 95% CI, -19.6 to 58.2; P=0.097). Cardiac mortality was not significant between amiodarone and the placebo groups (44 vs 55 patients respectively; RR reduction 22.0; 95% CI, -15.9 to 47.6; P=0.108). All-cause mortality was not significant between the amiodarone and placebo groups (57 vs 68 patients respectively; RR reduction, 18.3; 95% CI, -16.1 to 42.6; P=0.129).
Julian et al.[18] (1997) EMIAT Amiodarone 800 mg daily for 2 weeks, followed by 400 mg/day for 14 weeks, followed by 200	DB, MC, PC, RCT Patients 18 to 75 years who survived ≥5 days post documentation of an MI, LVEF of ≤40% on MUGA done 5 to 21 days after admission to the	N=1,486 2 years	Primary: All-cause mortality Secondary: Cardiac mortality, AD and AD plus resuscitated cardiac arrest	Primary: There was not a significant difference in all-cause mortality between the amiodarone and placebo groups (102 vs 103 patients in group; risk ratio, 0.99; 95% CI, 0.76 to 1.31; P=0.96). Secondary: There was not a significant difference in total cardiac mortality between the amiodarone and placebo groups (89 vs 85 patients; risk ratio, 0.94; 95% CI, 0.70 to 1.26; P=0.67).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day until the end of the trial vs placebo	coronary-care unit			The amiodarone group had a lower number of patients who experienced an AD compared to the patients in the placebo group (50 vs 33 patients; risk ratio, 0.65; 95% CI, 0.42 to 1.00; P=0.05). The amiodarone group had a lower number of patients who experienced an AD and resuscitated cardiac arrest compared to the patients in the placebo group (61 vs 42 patients; risk ratio, 0.68; 95% CI, 0.46 to 1.00; P=0.05).
Deedwania et al.[19] (1998) CHF-STAT Amiodarone 800 mg QD for 2 weeks, followed by 400 mg QD for 50 weeks, followed by 300 mg QD vs placebo	DB, MC, PC Patients with history of heart failure (≥3 months), NYHA class II, III, or IV, LVEF ≤40%, evidence of dilated cardiomyopathy, dyspnea on exertion or history of paroxysmal nocturnal dyspnea, and frequent ventricular premature beats on 24-hour Holter monitoring	N=667 4.5 years	Primary: Rate control vs conversion to sinus rhythm in atrial fibrillation patients Secondary: Occurrence of new atrial fibrillation	Primary: From time points at two weeks and beyond, the ventricular rates of those patients in the amiodarone treatment group were significantly lower than those in the placebo group (P=0.001 at week 2, and P=0.006 at months 6 and 12). Of the patients that had AF at baseline, 16 patients in the amiodarone group compared to four patients in the placebo group, spontaneously converted to sinus rhythm (P=0.002). Secondary: Eleven patients in the amiodarone group compared 22 patients in the placebo group experienced new-onset AF (P=0.005). Patients in the amiodarone group who spontaneously converted to sinus rhythm and maintained it during the follow-up period had significantly lower mortality compared to those who remained in AF (P=0.04).
Kochiadakis et al.[20] (2004) Amiodarone 15 mg/kg QD for 7 days, followed by 10 mg/kg QD for 7 days, then tapered dose over 7 to 12 days to maintenance levels	RCT, SB Patients >18 years of age, ECG documentation of AF, symptoms such as light-headedness, palpitation, chest pain, and dyspnea in association with AF; successful chemical or	N=146 3 years	Primary: Time to adverse events (relapse to AF or intolerable side effects), whichever occurred first Secondary: Maintenance of AF free time	Primary: There was not a significant difference between the amiodarone and propafenone groups for the suppression of recurrent symptomatic AF or in side effects (P=0.44). Secondary: Amiodarone and propafenone were equally effective in maintaining sinus rhythm without side effects included (P=0.058).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
over 7 to 12 days to a maintenance dose of 200 mg QD vs propafenone 150 to 300 mg followed by a maintenance dose of 150 mg TID	electrical cardioversion to sinus rhythm in the patients with persistent AF			
Gulizia et al.[21] (2008) PITAGORA Amiodarone 600 mg/day for 10 days, followed by 400 mg/day for 10 days, followed by 200 mg/day thereafter vs class Ic antiarrhythmic drugs (flecainide 200 mg/day, propafenone 450 to 600 mg/day)	MC, RCT, SB Patients with SND, ≥3 episodes of symptomatic AT in the 12 months before enrollment, and ≥1 AT episode documented by ECG or Holter recording	N=176 21 months	Primary: Composite of death, permanent AT, cardiovascular hospitalization, atrial cardioversion, or interruption of the randomly assigned antiarrhythmic drug regimen Secondary: AT-related composite end point (permanent AT, hospitalizations due to AT recurrences, atrial cardioversions, and assigned antiarrhythmic drug discontinuation	Primary: The primary end point occurred in 30.7% of patients in the class Ic group and 40.0% of patients in the amiodarone group (P=0.24). Secondary: Death occurred in 2.7% of patients receiving class Ic agents and 8.6% of patients receiving amiodarone (P=0.16). Twelve patients receiving amiodarone were hospitalized for cardiovascular causes compared to nine patients receiving class Ic drugs. Ischemic stroke occurred in two amiodarone patients. After one year, the AT-related composite end point was 22% for amiodarone and 22% for class Ic agents (23% for propafenone and 21% for flecainide; P=0.1). After one year, freedom from AT episodes at >10 minutes, one day, and seven days was 40, 73, and 91%, respectively, for amiodarone and 28, 78, and 86%, respectively for class Ic agents. The mean number of AT-related symptoms at the baseline was 2.0 in the amiodarone group and 2.2 in class Ic group. At the first follow-up visit, the mean number of AT-related symptoms decreased to 0.7 and 1.1, respectively (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			because of lack of efficacy), AT-related symptoms, QOL	QOL scores improved from baseline values of 52 in the amiodarone group and 54 in the class Ic group to 67 and 67, respectively, at the first follow-up visit (P<0.01). There was no significant difference between the treatment groups with regards to AT-related symptoms and QOL scores.
Kojuri et al.[22] (2009) Amiodarone 200 mg BID from 7 days before surgery to 5 days post surgery vs propranolol 20 mg BID from 7 days before surgery to 5 days post surgery vs amiodarone 200 mg BID plus propranolol 20 mg BID from 7 days before surgery to 5 days post surgery	DB, PRO, RCT Patients who underwent elective CABG	N=240 12 days	Primary: Percentage of patients who developed post-CABG AF Secondary: Not reported	Primary: Post-CABG AF developed in 22 patients (9.2%), of whom 13 (16.3%) received propranolol, five (6.3%) received amiodarone and four (5.0%) received combination therapy. The difference in AF between propranolol and amiodarone monotherapy was significant (P=0.02), but not between either monotherapy with combination therapy (P=0.6 and P=0.76). The duration of AF episodes was <24 hours in four patients (80%) receiving amiodarone, nine patients (69.2%) receiving propranolol and four patients (100%) receiving combination therapy (P values not reported). Secondary: Not reported
Piccini et al.[23] (2014) Amiodarone vs sotalol	RETRO Patients with CAD and AF	N=2,838 Median follow-up 4.2 years	Primary: All-cause mortality Secondary: Not reported	Primary: In unadjusted and adjusted settings, mortality rates were lower in patients treated with sotalol compared with amiodarone or no AAD. After adjustment for baseline characteristics only, the 1-year mortality rate was 10% in those treated with sotalol, 20% in those treated with amiodarone, and 14% in those treated with no AAD (no P-value reported). Landmark analysis at 60 days and one year was also performed. After

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs no antiarrhythmic drug (AAD)				adjustment and weighting, sotalol was associated with improved survival from 0 to 60 days compared with amiodarone (HR, 0.14; 95% CI, 0.06 to 0.32) but not at later time points (≥60 days or ≥1 year). Similarly, compared with no AAD therapy, sotalol was not associated with improved survival beyond 60 days. Cumulative survival after one year in patients treated with sotalol vs no AAD was also not improved (P=0.64). Secondary: Not reported
Lee et al.[24] (2008) Amiodarone vs sotalol vs beta-blockers (agents not specified) Doses of the agents were not specified.	RETRO Patients with AF and/or CHF (NYHA class ≥III) and an implantable cardioverter defibrillator	N=55 2.6±2.0 years	Primary: Cumulative rates of inappropriate shocks Secondary: Not reported	Primary: Amiodarone demonstrated a significantly lower rate of inappropriate shock compared to the beta-blockers (27.3 vs 70.6% at four years; P=0.003). This demonstrated an 83% reduction compared to the beta-blockers (HR, 0.17; 95% CI, 0.05 to 0.64; P=0.008). There was not a significant difference in rates of inappropriate shocks observed between the amiodarone and sotalol groups (27.3 vs 54.3% at four years; P=0.29). There was not a significant difference in rates of inappropriate shocks observed between the sotalol and beta-blocker groups (54.3 vs 70.6% at four years; P=0.16). Secondary: Not reported
Connolly et al.[25] (2006) OPTIC Beta-blocker (bisoprolol, carvedilol or metoprolol) vs	DB, MC, RCT Patients who received an implantable cardioverter defibrillator within 21 days of randomization, had sustained	N=412 12 months	Primary: Implantable cardioverter defibrillator shock for any reason Secondary: Not reported	Primary: Shocks occurred in 41 patients (38.5%) in the beta-blocker group, 26 (24.3%) patients in the sotalol group, and 12 (10.3%) patients in the amiodarone plus beta-blocker group. A reduction in the risk of shock was observed with use of amiodarone plus beta-blocker or sotalol vs beta-blocker alone (HR, 0.44; 95% CI, 0.28 to 0.68; P<0.001). The amiodarone plus beta-blocker group significantly reduced the risk of

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sotalol 240 mg/day in 2 to 3 divided doses vs amiodarone 200 mg/day plus β-blocker (bisoprolol, carvedilol or metoprolol) Amiodarone was loaded at 400 mg BID for 2 weeks, followed by 400 mg/day for 4 weeks, and then 200 mg/day until then end of the study	ventricular tachycardia, ventricular fibrillation or cardiac arrest (not ≤72 hours of acute MI), LVEF ≤40%, inducible ventricular tachycardia or ventricular fibrillation by programmed ventricular stimulation with LVEF ≤40% or unexplained syncope with ventricular tachycardia or ventricular fibrillation, inducible by programmed stimulation			shock compared to the beta-blocker alone group (HR, 0.27; 95% CI, 0.14 to 0.52; P<0.001) and the sotalol group (HR, 0.43; 95% CI, 0.22 to 0.85; P=0.02). The sotalol group did not significantly reduce the risk of shock compared to the beta-blocker alone group (HR, 0.61; 95% CI, 0.37 to 1.01; P=0.055). Secondary: Not reported
Torp-Pederson et al.[26] (1999) Dofetilide 250 µg QD to 500 µg BID vs placebo	DB, MC, PC, RCT Patients ≥18 years hospitalized with new or worsening CHF and who had ≥1 episode of shortness of breath on minimal exertion or at rest or paroxysmal nocturnal dyspnea	N=1,518 1 year	Primary: Death from any cause Secondary: Death from cardiac causes, death from arrhythmia, death from cardiac causes or successful resuscitation after	Primary: Death did not differ significantly between dofetilide treatment group and placebo (311 [41%] vs 317 [42%] respectively; HR, 0.95; 95% CI, 0.81 to 1.11; P=0.54). Secondary: There was not a significant difference in death from cardiac causes between dofetilide treatment group and placebo (33 vs 33%, respectively). There was not a significant difference in death from arrhythmias between dofetilide treatment group and placebo (20 vs 20%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cardiac arrest, arrhythmias requiring treatment, worsening CHF and MI, and in patients with baseline AF, incidence of conversion to and maintenance of sinus rhythm	Fewer hospitalizations due to worsening heart failure were experienced in the dofetilide group compared to placebo (30 vs 38%, respectively). There was a significant greater number of patients with AF at baseline who converted to sinus rhythm in the dofetilide compared to those patients with AF at baseline in the placebo group. At one month: 12 vs 2%, respectively (P<0.001) and at 12 months: 44 vs 13%, respectively (P<0.001). After cardioversion, more patients with baseline AF in the dofetilide group maintained sinus rhythm compared to those patients in the placebo group (HR, 0.35; 95% CI, 0.22 to 0.57; P<0.001).
Singh et al.[27] (2007) EURIDIS and ADONIS Dronedarone 400 mg BID vs placebo	DB, MC, RCT Patients ≥21 years of age with ≥1 episode of AF in the preceding 3 months who were in sinus rhythm for ≥1 hour before randomization	N=1,237 1 year	Primary: Time from randomization to the first documented recurrence of AF Secondary: Symptoms related to AF during recordings of 12-lead electro-cardiography or transtelephonic monitoring and the mean ventricular rate during the first recurrence	Primary: In EURIDIS, the median times from randomization to a documented recurrence of AF were 96 days in the dronedarone group and 41 days in the placebo group. At 12 months, 67.1% of patients in the dronedarone group and 77.5% of patients in the placebo group had had a recurrence of atrial fibrillation (HR, 0.78; 95% CI, 0.64 to 0.96; P=0.01). In ADONIS, the median times from randomization to a documented recurrence of AF were 158 days in the dronedarone group and 59 days in the placebo group. At 12 months, 61.1% of patients in the dronedarone group and 72.8% of patients in the placebo group had had a recurrence of AF (HR, 0.73; 95% CI, 0.59 to 0.89; P=0.002). In the combined analysis, the median times to a documented recurrence of AF were 116 days in the dronedarone group and 53 days in the placebo group. At 12 months, the rates of recurrence were 64.1% in the dronedarone group and 75.2% in the placebo group (HR, 0.75; 95% CI, 0.65 to 0.87; P<0.001). Secondary: In EURIDIS, 37.1% of patients in the dronedarone group and 47.5% of those in the placebo group had symptomatic recurrences of AF (P=0.006). In ADONIS, symptomatic recurrences occurred in 38.3% of patients in the dronedarone group and 44.5% of those in the placebo group (P=0.02). In the combined analysis, the corresponding numbers were 37.7 and 46.0%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.001). In EURIDIS, the mean ventricular rate during the first adjudicated recurrence was 102.3beats per minute in the dronedarone group and 117.5 beats per minute in the placebo group (P<0.001). In ADONIS, the mean ventricular rate during the first adjudicated recurrence was 104.6 beats per minute in the dronedarone group and 116.6 beats per minute in the placebo group (P<0.001). In EURIDIS, 21.2% of patients in the dronedarone group were hospitalized or died at 12 months compared to 32.0% of those in the placebo group (HR, 0.66; 95% CI, 0.47 to 0.93; P=0.02). In ADONIS, 24.5% of patients in the dronedarone group were hospitalized or died compared to 29.8% of those in the placebo group (HR, 0.80; 95% CI, 0.56 to 1.14; P=0.22). In the combined analysis, the corresponding numbers were 22.8 and 30.9% (HR, 0.73; 95% CI, 0.57 to 0.93; P=0.01). There was a higher incidence of elevated serum creatinine levels in the dronedarone group than in the placebo group (2.4 vs 0.2%, P=0.004). Ventricular arrhythmias occurred infrequently in both groups and no episodes of torsades de pointes were reported.
Hohnloser et al.[28] (2009) ATHENA Dronedarone 400 mg BID vs placebo	DB, MC, PC, RCT Patients with paroxysmal or persistent AF or atrial flutter with ≥1 of the following risk factors: ≥70 years of age, arterial hypertension (treated with ≥2 antihypertensive drugs), diabetes mellitus, previous stroke, TIA, or systemic embolism,	N=4,628 21 months	Primary: First hospitalization due to cardiovascular events or death Secondary: Death from any cause, death from cardiovascular causes, hospitalization due to cardiovascular events	Primary: In the dronedarone group, 31.9% of patients experienced the primary outcome compared to 39.4% of patients in the placebo group (HR, 0.76; 95% CI, 0.69 to 0.84; P<0.001). Secondary: Death from any cause occurred in 5.0% of patients in the dronedarone group and 6.0% of patients in the placebo group (HR, 0.84; 95% CI, 0.66 to 1.08; P=0.18). Cardiovascular death occurred in 2.7% of patients in the dronedarone group and 3.9% of patients in the placebo group (HR, 0.71; 95% CI, 0.51 to 0.98; P=0.03). In the dronedarone group, 29.3% of patients had a first hospitalization due to cardiovascular events compared to 36.9% of patients in the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	left atrial diameter ≥50 mm, and LVEF ≤40%			group (HR, 0.74; 95% CI, 0.67 to 0.82; P<0.001). Bradycardia, QT-interval prolongation, diarrhea, nausea, rash, and an increase in the serum creatinine level were significantly more common in the dronedarone group than in the placebo group. Pulmonary symptoms, interstitial lung disease, and abnormalities of thyroid function were not significantly more common with dronedarone than with placebo.
Page et al.[29] (2011) ATHENA Dronedarone 400 mg BID vs placebo Randomization was stratified according to sinus rhythm status at baseline	Post-hoc analysis of ATHENA Patients with paroxysmal or persistent AF or atrial flutter and additional cardiovascular risk factors, and a 12-lead ECG <6 months before randomization available showing AF or atrial flutter, and a second 12-lead ECG within the same time period had to show sinus rhythm	N=3,473 (patients in sinus rhythm at baseline) 21 months	Primary: Time to first AF or atrial flutter recurrence, incidence of electrical cardioversion, likelihood of permanent AF and atrial flutter Secondary: Not reported	Primary: The median time to first AF or atrial flutter recurrence of patients in sinus rhythm at baseline was 498 and 737 days with placebo and dronedarone (HR, 0.749; 95% CI, 0.681 to 0.824; P<0.001). At the time of first AF and atrial flutter recurrence, the mean heart rates were 85.3 and 95.5 bpm with dronedarone and placebo, respectively (P<0.001). Three hundred and thirty nine patients (15%) receiving dronedarone had at least one electrical cardioversion compared to 481 (21%) patients receiving placebo (HR, 0.684; 95% CI, 0.596 to 0.786; P<0.001). The likelihood of permanent AF and atrial flutter was lower with dronedarone (7.6 vs 12.8% of patients; HR, 0.749; 95% CI, 0.681 to 0.824; P<0.001). Secondary: Not reported
Torp-Pedersen et al.[30] (2011) ATHENA Dronedarone 400 mg BID vs	Post-hoc analysis of ATHENA Patients with paroxysmal or persistent AF or atrial flutter with ≥1 of the following risk factors: ≥70 years of age, arterial	N=4,628 21 months	Primary: Number of first hospitalizations per treatment group, number of hospitalizations after first AF/atrial flutter recurrence, number of all hospitalizations,	Primary: Overall, the number of first cardiovascular hospitalizations was significantly decreased with dronedarone compared to placebo (675 vs 859 patients; HR, 0.74; 95% CI, 0.67 to 0.82; P<0.001). There was no difference between the number of first non-cardiovascular hospitalizations between the two treatments (516 vs 533; P=0.77). Among the patients experiencing at least one AF-related hospitalization during the trial, 50% remained in the hospital for at least four nights and 25% for at least eight nights. The total number of hospitalizations for AF

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placebo	hypertension (treated with ≥2 antihypertensive drugs), diabetes mellitus, previous stroke, TIA, or systemic embolism, left atrial diameter ≥50 mm, and LVEF ≤40%		duration of hospital stay, hospitalization burden over time Secondary: Not reported	was reduced from 829 with placebo to 514 with dronedarone (HR, 0.626; 95% CI, 0.546 to 0.719; P<0.001) and the number of days in hospital from 4,637 to 3,132, respectively (P<0.001). Dronedarone significantly reduced total hospitalizations for acute coronary syndrome (73 vs 113; P=0.0105) and the number of hospitalization days (816 vs 1,188 days; P=0.04). Dronedarone significantly reduced the time between the first AF/atrial flutter recurrence and cardiovascular hospitalization/death (HR, 0.771; 95% CI, 0.643 to 0.925; P=0.0048). Hospitalization burden was significantly reduced across all levels of care (P<0.05). Secondary: Not reported
Duray et al.[31] (2011) ATHENA/ EURIDIS/ ADONIS Dronedarone 400 mg BID vs placebo	Pooled post-hoc analysis of ATHENA/ EURIDIS/ADONIS trials Individual patients with lone AF who were enrolled in the ATHENA, EURIDIS, and ADONIS trials were entered in a center database	N=432 13.8±7.2 months	Primary: Composite of cardiovascular hospitalizations or death, and the individual components Secondary: Not reported	Primary: The risk of first cardiovascular hospitalizations or all-cause mortality in patients receiving placebo after one year was 25% in the lone AF group compared to 29% in the rest of the population. In patients with lone AF, dronedarone led to a 44% reduction in cardiovascular hospitalizations or all-cause mortality (HR, 0.56; 95% CI, 0.36 to 0.88; P=0.004) and to a 46% reduction in cardiovascular hospitalization (HR, 0.54; 95% CI, 0.34 to 0.87; P=0.004) compared to placebo. There was no significant difference between dronedarone and placebo with regards to all-cause mortality (HR, 1.02; 95% CI, 0.31 to 3.34; P=0.885). Secondary: Not reported
Kober et al.[32] (2008) ANDROMEDA Dronedarone 400 mg BID	DB, MC, PC, PG, RCT Patients ≥18 years of age who were hospitalized with	N=627 An average of 62.1 days and a median follow-up of 2	Primary: Composite of death from any cause or hospitalization for worsening heart failure	The study terminated prematurely due to increased death in the active treatment group. During a median follow-up of two months, 25 (8.1%) patients in the dronedarone group and 12 (3.8%) patients in the placebo group died (HR, 2.13; 95% CI, 1.07 to 4.25; P=0.03). After an additional six months without study treatment, 42 (13.5%)

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vs placebo	new or worsening heart failure and who had ≥1 episode of shortness of breath on minimal exertion (NYHA functional class III or IV) or paroxysmal nocturnal dyspnea within the month before screening	months	Secondary: Death from all causes, hospitalization for cardiovascular causes, hospitalization for worsening heart failure, occurrence of AF/atrial flutter, death from arrhythmia, or sudden death	patients in the dronedarone group and 39 (12.3%) patients in the placebo group died (HR, 1.13; 95% CI, 0.73 to 1.71; P=0.60). Subgroup analysis of the study population, after adjustment for risk factors, showed that the most powerful predictor of death was treatment with dronedarone (HR, 2.19; 95% CI, 1.06 to 4.52; P=0.03). Primary: The primary composite endpoint was not significantly different between groups (17.1% [53 events] for dronedarone vs 12.6% [40 events] for placebo; HR, 1.38; 95% CI, 0.92 to 2.09; P=0.12). After an additional six months of follow-up after treatment discontinuation, 74 patients (23.9%) and 72 patients (22.7%) in the dronedarone and placebo groups, respectively, had reached the primary composite endpoint (HR, 1.09; 95% CI, 0.79 to 1.51; P=0.60). Secondary: First hospitalization for cardiovascular cause was higher in the dronedarone group than the placebo group (71 vs 50; P=0.02) with the main reason being worsening heart failure (49.3% for the dronedarone group and 60.0% for the placebo group). Other reasons for hospitalization for cardiovascular causes included MI (18.3 and 16.0%; in the dronedarone and placebo groups, respectively), ventricular arrhythmia (4.2 and 4.0%), supraventricular arrhythmia (5.6 and 2.0%), stroke (5.6 and 6.0%), other cardiovascular events (12.7 and 8.0%), and presumed cardiovascular events (4.2 and 4.0%). At one month, there was no significant difference between the two groups in the percentage of patients who had AF (21.4% for the dronedarone group vs 24.8% for the placebo group; P value not reported). Ten (3.2%) patients and six (1.9%) patients in the dronedarone and placebo groups died from arrhythmia or sudden death during the double-blind, randomized study period. This difference was not significantly different (P value not reported).
Touboul et al.[33]	DB, PC, RCT	N=270	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) DAFNE Dronedarone 400 mg BID vs dronedarone 600 mg BID vs dronedarone 800 mg BID vs placebo	Patients 21 to 85 years of age with persistent AF for whom cardioversion and antiarrhythmic treatment was warranted	6 months	Time to first documented AF recurrence Secondary: Spontaneous conversion of AF following randomization, heart rate in case of AF recurrence, and incidence of side effects	Only in the 400 mg twice daily arm was the time to AF relapse significantly different from placebo (60.0 vs 5.3 days; RR reduction, 55%; 95% CI, 72 to 28; P=0.001). Secondary: There was a dose-effect relationship to the incidence of spontaneous conversion to sinus rhythm (P=0.0261) with patients in all dronedarone groups (400, 600, and 800 mg) exhibiting spontaneous conversion to sinus rhythm (5.8, 8.2 and 14.8%, respectively, vs 3.1% for the placebo group). Dronedarone appeared to slow ventricular rate during AF recurrence in a dose-dependent manner. The rate was reduced by 13.2, 19.2 and 17.8 bpm vs placebo (P=0.0001). Discontinuation rates due to adverse events were 10.8% with dronedarone treated patients (3.9, 7.6 and 22.6%, respectively) vs 0% with placebo treated patients (P value not reported). Most commonly reported effects were gastrointestinal related.
Davy et al.[34] (2008) ERATO Dronedarone 400 mg BID vs placebo	DB, MC, PC, RCT Adult patients ≥21 years with documented, symptomatic permanent AF, for which cardioversion was not considered an option	N=174 6 months	Primary: Change in mean ventricular rate measured by 24-hour Holter recording on day 14 Secondary: Change in mean ventricular rate during submaximal and maximal exercise at day 14, change in maximal exercise duration at day 14, change in mean	Primary: There was a mean reduction in mean 24-hour ventricular rate of 11.0 beat/min in the dronedarone group at day 14 compared to an increase of 0.7 beat/min in the placebo group (P<.0001). Secondary: There was a reduction in mean heart rate of 25.6 beat/min in the dronedarone group compared to 2.2 beat/min in the placebo group during submaximal exercise (P<0.0001). There was a reduction in mean heart rate of 27.4 beat/min in the dronedarone group compared to 2.9 beat/min in the placebo group at maximal exercise (P<0.0001). There was a mean increase in maximal exercise duration of 0.14 and 0.26 minutes in the dronedarone and placebo groups, respectively (P=0.514). The mean change in 24-hour Holter-monitored ventricular heart rate was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			ventricular rate measured by 24-hour Holter after 4 months, safety and tolerability	greater with dronedarone compared to placebo at four months (-10.1 vs -1.3 beat/min, respectively; P<0.001). Dronedarone was well tolerated throughout the study. There were no cases of torsades de pointes or sustained ventricular tachycardia reported in either treatment group. The incidence of treatment-emergent adverse events was higher with dronedarone than placebo. Gastrointestinal disturbances occurred in 20% of patients receiving dronedarone compared to 13.5% of those receiving placebo.
Køber et al.[35] (2008) ANDROMEDA Dronedarone 400 mg BID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age who were hospitalized with new or worsening heart failure and who had had ≥1 episode of shortness of breath on minimal exertion or at rest (NYHA III or IV), paroxysmal nocturnal dyspnea, or a wall-motion index ≤1.2	N=627 7 months	Primary: Death from any cause or hospitalization for worsening heart failure Secondary: Death from all causes, hospitalization for cardiovascular causes, hospitalization for worsening heart failure, occurrence of AF or atrial flutter, death from arrhythmia, or sudden death	Primary: The data and safety monitoring board recommended that the trial be terminated early due to an excess of deaths in the dronedarone group. Death from any cause occurred in 8.1% of patients receiving dronedarone and 3.8% of patients receiving placebo (HR, 2.13; 95% CI, 1.07 to 4.25; P=0.03). The number of deaths that were attributed to arrhythmia or sudden death did not differ significantly between the two groups. The primary combined end point of all-cause mortality or hospitalization for worsening heart failure was not different between dronedarone and placebo (17.1 vs 12.6%, respectively; HR, 1.38; 95% CI, 0.92 to 2.09; P=0.12). Secondary: The total number of patients who had a first hospitalization for an acute cardiovascular cause was higher in the dronedarone group than in the placebo group (P=0.02). The main reason for hospitalization for a cardiovascular cause was worsening heart failure (49.3% in the dronedarone group and 60.0% in the placebo group). Other cardiovascular events requiring a first hospitalization in the dronedarone group compared to placebo were myocardial ischemia (18.3 vs 16.0%, respectively), ventricular arrhythmia (4.2 vs 4.0%, respectively), supraventricular arrhythmia (5.6 vs 2.0%, respectively), stroke (5.6 vs 6.0%, respectively), other cardiovascular events (12.7 vs 8.0%, respectively), and presumed cardiovascular events (4.2 vs 4.0%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences detected between the two groups with regards to serious adverse events, except for increases in the serum creatinine concentration, which were observed more frequently in the dronedarone group than in the placebo group. At the one month visit, 21.4% of the patients in the dronedarone group had AF compared to 24.8% of patients receiving placebo (P value not significant). No cases of torsades de pointes were observed in either group.
Connolly et al.[36] (2011) PALLAS Dronedarone 400 mg BID vs placebo	DB, MC, PC, RCT Patients ≥65 years of age with ≥6 month history of permanent AF or atrial flutter and risk factors for major vascular events (coronary artery disease; pervious stroke or TIA; symptomatic heart failure; LVEF ≤40%; peripheral arterial disease; or the combination of age ≥75 years, hypertension, and diabetes)	N=3,236 1 year	Primary: Composite of stroke, MI, systemic embolism, or death from cardiovascular causes; composite of unplanned hospitalization for a cardiovascular cause or death Secondary: Safety	After enrollment of 3,236 patients the trial was stopped for safety reasons. Primary: The first coprimary endpoint (composite of stroke, MI, systemic embolism, or death from cardiovascular causes) occurred in 43 and 19 patients receiving dronedarone and placebo (HR, 2.29; 95% CI, 1.34 to 3.94; P=0.002). There were 21 and 10 cardiovascular deaths with dronedarone and placebo (HR, 2.11; 95% CI, 1.00 to 4.49; P=0.046), including death from arrhythmia in 13 and four patients, respectively (HR, 3.26; 95% CI, 1.06 to 10.0; P=0.03). Stroke occurred in 23 and 10 patients receiving dronedarone and placebo (HR, 2.32; 95% CI, 1.11 to 4.88; P=0.02). Hospitalization for heart failure occurred in 43 and 24 patients receiving dronedarone and placebo (HR, 1.81; 95% CI, 1.10 to 2.99; P=0.02). Secondary: The most common adverse events were diarrhea, asthenic condition, nausea and vomiting, dizziness, dyspnea, and bradycardia. An increase of alanine aminotransferase of more than three times the upper limit of normal range occurred in 1.5 and 0.6% of patients receiving dronedarone and placebo (P=0.013).
Ezekowitz et al.[37] (2015) HESTIA	DB, MC, PC, RCT Patients ≥21 years of age with	N=112 12 weeks	Primary: Change in AF burden from baseline over the	Primary: Over the 12-week treatment period, mean AF burden increased from 8.8% to 9.9% (increase of 12.8%; P=0.450) in the placebo group and decreased from 10.1% to 4.6% (decrease of 54.4%; P=0.0009) in the dronedarone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dronedarone 400 mg BID vs placebo	documented AF with a permanent pacemaker and sinus rhythm within the previous six months		12-week treatment period Secondary: Patient-perceived AF burden; and symptom severity as reported by patients using the Atrial Fibrillation Severity Scale (AFSS)	group. The absolute changes in AF burden from baseline increased by 1.1% in the placebo group and decreased by 5.5% in the dronedarone group. Compared to placebo, AF burden in the dronedarone group was decreased by 59.1% (P=0.0015). Secondary: AF burden changes with dronedarone compared to placebo in secondary efficacy analyses were consistent with the overall result (weeks 1 to 4, 63.2% reduction, P=0.0009; weeks 5 to 12, 60.3% reduction, P=0.003). AFSS changes from baseline were not significantly different between groups.
Le Huezey et al.[38] (2010) DIONYSOS Dronedarone 400 mg BID vs amiodarone 600 mg/day for 28 days then 200 mg/day thereafter	DB, MC, PG, RCT Patients ≥21 years of age with documented AF for >72 hours, for whom antiarrhythmic drugs and cardioversion were indicated, and who received oral anticoagulation	N=504 6 months	Primary: Composite of time to first AF recurrence or premature study drug discontinuation for intolerance or lack of efficacy, and safety evaluation of occurrence of thyroid, hepatic, pulmonary, neurological, skin, ocular, or gastrointestinal events or premature drug discontinuation following an adverse event Secondary: Not reported	Primary: At 12 months the incidence of the primary composite endpoint was 75.1% in the dronedarone group and 58.8% in the amiodarone group (HR, 1.59; 95% CI, 1.28 to 1.98; P<0.0001). The crude rates of the components of the primary composite endpoints of AF recurrence compared to premature study drug discontinuation was 63.5 vs 10.4% in the dronedarone group and 42.0 vs 13.3% in the amiodarone group. This demonstrates that the primary endpoint was mainly driven by AF recurrence. In the AF recurrence component of the endpoint, AF after electrical cardioversion occurred in 36.5 and 24.3% of patients in the dronedarone and amiodarone groups, respectively (P value not reported). At 12 months the incidence of the primary safety endpoint was 39.3% in the dronedarone group and 44.5% in the amiodarone group (HR, 0.8; 95% CI, 0.60 to 1.07; P=0.129). The difference between the two groups was mainly driven by increased thyroid, neurologic, skin, and ocular events in the amiodarone group. There was a higher incidence of gastrointestinal events, mainly diarrhea in the dronedarone group (9.2%) compared to the amiodarone group (3.1%). A pre-specified endpoint of the main safety event excluding gastrointestinal effects showed a 39% RR reduction in favor of dronedarone (HR, 0.61; 95% CI, 0.44 to 0.84; P=0.002). When the components of the main safety events were analyzed separately, there was a RR reduction of 84.2% (P=0.0006) in the incidence of thyroid events and 87.6% (P=0.0001) in the incidence of neurologic events favoring dronedarone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Piccini et al.[39] (2009) Dronedarone 400 mg BID vs amiodarone 200 mg QD	MA Patients with AF	N=7,140 13 to 16 months (mean duration)	Primary: Recurrence of AF, all-cause mortality, adverse events Secondary: Not reported	Primary: *Dronedarone vs placebo* For prevention of AF, the effect of dronedarone had an OR of 0.79 (95% CI, 0.33 to 1.87), with a risk difference of -0.040 (95% CI, -0.19 to 0.11) equivalent to 40 fewer events per 1,000 patients treated. For mortality, the OR was 0.85 (95% CI, 0.66 to 1.11), with a risk difference of -0.003 (95% CI, -0.011 to 0.006). For adverse events requiring discontinuation, there was a significant increase over placebo with OR of 1.166 (95% CI, 1.36 to 2.02) and risk difference 0.045 (95% CI, 0.028 to 0.062). *Amiodarone vs placebo* Amiodarone significantly prevented AF, with an OR of 0.12 (95% CI, 0.08 to 0.19) and a risk difference of -0.401 (95% CI, -0.46 to -0.34) equivalent to 401 fewer events per 1,000 patients treated. For mortality, the OR was 1.88 (95% CI, 0.54 to 6.56), with a risk difference of 0.005 (95% CI, -0.016 to 0.026). For adverse events requiring discontinuation, there was a significant increase over placebo with an OR of 11.04 (95% CI, 1.89 to 64.5) and risk difference of 0.128 (95% CI, 0.023 to 0.230). *Dronedarone vs amiodarone* In the indirect MA, amiodarone significantly reduced the risk of recurrent AF compared to dronedarone (OR, 0.16; 95% CI, 0.06 to 0.42), with a risk difference of -0.36 (95% CI, -0.52 to -0.19), which is equivalent to 360 fewer events per 1,000 patients treated. This was consistent with the direct results from DIONYSOS (OR, 0.44; 95% CI, 0.30 to 0.64), with a risk difference of -0.186 (95% CI, -0.266 to -0.1028).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a mortality trend favoring dronedarone in the indirect MA (amiodarone vs dronedarone OR, 2.20; 95% CI, 0.61 to 7.88; risk difference: 0.008; 95% CI: -0.015 to 0.030). This finding was consistent with the DIONYSOS trial (OR, 2.44; 95% CI, 0.48 to 12.6), risk difference 0.011 (95% CI, -0.010 to 0.033). For adverse effects requiring interruption of therapy, the indirect MA estimate favored dronedarone; amiodarone was associated with an increased odds of study drug termination (OR, 6.65; 95% CI, 1.13 to 39.3) with a risk difference of 0.083 (95% CI, -0.022 to 0.1866). The effect was similar in DIONYSOS (OR, 2.24; 95% CI, 1.13 to 4.43) with a risk difference of 0.057 (95% CI, 0.010 to 0.105). The incidence of thyroid toxicity (4 vs 3%), symptomatic bradyarrhythmias (2.8 vs 1.1%), and hepatotoxicity (3.5 vs 2.5%) leading to treatment discontinuation were comparable between dronedarone and placebo. There were no cases of torsades de pointes in any of the patients administered amiodarone or in the DIONYSOS trial. There was a single case of torsades de pointes in a patient receiving dronedarone in ATHENA. Secondary: Not reported
Kirchhof et al.[40] (2012) Flec-SL Flecainide 200 to 300 mg/day for 4 weeks vs flecainide 200 to 300 mg/day for 6 months	Blinded endpoint, MC, OL, PRO, RCT Adults with persistent AF undergoing planned cardioversion	N=635 6 months	Primary: Time to persistent AF or death, QOL Secondary: Safety	Primary: The first analysis performed with the four week follow-up data for 242 patients, and demonstrated that flecainide (short- and long-term treatment combined) was superior to no treatment (control; 28-day Kaplan-Meier survival of 70.2% [95% CI, 63.0 to 77.3] of patients receiving flecainide vs 52.5% [95% CI, 41.4 to 63.6] of patients receiving control; P=0.0160). On the basis of these findings, an additional analysis was conducted to compare short-term and long-term maintenance treatment; enrollment into the control group ended, and sample size was adjusted from 725 to 635. In the per protocol population, 120 (46%) of 261 patients receiving short-term treatment developed persistent AF (48.4%; 95% CI, 41.9 to 55.0) vs 103 (39%) of 263 receiving long-term treatment (56.4%; 95% CI, 49.1 to 63.6). No deaths occurred. The difference between the two groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no treatment (control) Patients were randomized to trial medication after successful cardioversion.				receiving flecainide in the mean percentage of patients who did not have persistent AF was 7.9% (95% CI, -1.9 to 17.7); therefore, noninferiority of short-term to long-term treatment could not be shown (P=0.2081). In the intention-to-treat population, the difference between short-term and long-term treatment was 6.3% (95% CI, -2.6 to 15.3; P=0.1073). In a post-hoc analysis of patients who had not reached the primary endpoint in the first month confirmed that long-term treatment was superior to short-term treatment in the prevention of persistent AF or death (difference between Kaplan-Meier estimates 14.3%; 95% CI, 5.1 to 23.6; P=0.0001; HR, 0.31; 95% CI, 0.118 to 0.56; P<0.0001). QOL improved with short-term and long-term flecainide treatment. In the control group, only physical sores of the SF-12 improved, not mental. Number of admissions because of AF, number of medical visits without admission, left ventricular function at six months, and QOL did not differ between short-term and long-term treatment. Secondary: The number of serious adverse events was low with all treatments, and did not vary between treatments. The number did not differ between patients with coronary artery disease and those without the disorder.
Cast Investigators[41,42] (1993 and 1989) CAST I Encainide* 35 to 50 mg TID, flecainide 100 to 150 mg BID or moricizine* 200 to 250 mg TID vs placebo	MC, OL, PC, RCT Patients 6 days to 2 years post documented MI who had ≥6 VDPs per hour during an ambulatory ECG recording, and a LVEF of ≤55% if recorded 6 to 90 days after MI, or ≤40% if recorded 90 days to 2 years post-MI	N=2,371 1 year	Primary: Overall survival and free of cardiac arrest or AD Secondary: Not reported	Primary: After one year of therapy 90% of patients in the active treatment group survived compared to 95% of patients in the placebo group (P=0.0006). A higher total mortality rate was seen in the encainide and flecainide groups: 56 patients (7.7%) taking encainide or flecainide compared to 22 patients (3.0%) taking placebo (RR, 2.5; 95% CI, 1.6 to 4.5). After one year of therapy, 93% of patients in the active treatment group were free of cardiac arrest or AD compared to 96% of patients in the placebo group (P=0.003). Encainide and flecainide accounted for the excess of deaths from arrhythmia and nonfatal cardiac arrests: 33 patients (4.5%) taking encainide or flecainide compared to nine patients (1.2%) taking placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(RR, 3.6; 95% CI, 1.7 to 8.5). After a mean follow up of 10 months, due to a significantly higher death rate in the active treatment group (63 patients) compared to the placebo group (26 patients; P=0.000), the flecainide and encainide arms of this trial were stopped early. Also, death or cardiac arrest due to arrhythmia was significantly higher in the active treatment group (43 patients) compared to the placebo group (16 patients; P=0.0004).
Balla et al.[43] (2011) Flecainide 3 mg/kg, single dose vs amiodarone 30 mg/kg, single dose vs propafenone 8.5 mg/kg, single dose vs placebo	PC, PRO, RCT, SB Patients with recent AF	N=160 48 hours	Primary: Conversion rate at 24 hours after the drug intake Secondary: Safety	Primary: The primary endpoint occurred in 87.5, 85, 85, and 17.5% of patients receiving flecainide, amiodarone, propafenone, and placebo (P<0.001 vs placebo for all three comparisons). Conversion rates within three hours after drug intake was greater with propafenone (57.5%) or flecainide (45%) compared to amiodarone (0%) or placebo (10%). Between six and 24 hours, significantly more patients were converted to sinus rhythm with amiodarone compared to flecainide or propafenone. The use of antiarrhythmic drugs was a significant predictor of conversion to sinus rhythm compared to placebo (adjusted OR, 19.53; 95% CI, 3.14 to 121.55; P<0.001). Secondary: There were no significant adverse effects during the follow-up period in the drug arm. Two patients receiving amiodarone had mild diarrhea.
Kosior et al.[44] (2009) Propafenone 600 mg orally, followed by 300 mg after 8 hours if sinus rhythm had not been restored by	RCT Patients 18 to 85 years of age admitted to the Emergency Department with symptomatic recent onset AF <48 hours duration,	N=81 24 hours	Primary: Restoration of sinus rhythm, safety Secondary: Not reported	Primary: Within the first 24 hours, sinus rhythm was restored in 90.7% of patients receiving propafenone and in 91.4% of patients receiving digoxin/quinidine. There was no significant difference in the efficacy after 24 hours of follow-up (90.1 vs 91.4%, respectively; P=0.78). Propafenone was more effective at restoring sinus rhythm than digoxin/quinidine during the first eight hours (83.3 vs 54.3%, respectively; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
then vs digoxin 1 mg IV, followed by an oral loading of quinidine (400 mg, followed by 200 mg every 2 hours)	mean ventricular rate >70 beats per minute, and NYHA functional class <II			No life-threatening adverse events were reported during the follow-up. There was no difference in mild adverse events with propafenone compared to digoxin/quinidine (37.2 vs 45.7%, respectively; P=0.56). No case of significant heart failure exacerbation was observed. Secondary: Not reported
Wyse et al.[45] (2002) AFFIRM Rhythm control therapy: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm) vs rate control therapy: β-blockers, calcium-channel	MC, RCT Patients 65 years and older who had AF that was likely recurrent, AF was likely to cause illness or death, long-term treatment for AF was warranted, no contraindicated to anticoagulation therapy, eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after randomization	N=4,060 3.5 years	Primary: Overall mortality Secondary: Composite death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest	Primary: The difference in mortality between the two groups was not significant (HR, 1.15; 95% CI, 0.99 to 1.34; P=0.08). Secondary: The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest were also similar in the two groups (P=0.33).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
blockers, digoxin, and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm)				
Van Gelder et al.[46] (2002) RACE Rhythm control therapy: electrical cardioversion, then sotalol 160 to 320 mg (based on weight and renal function); if recurrence within 6 months, repeat electrical cardioversion, then flecainide 200 to 300 mg QD or propafenone 450 to 900 mg QD; if recurrence again, electrical cardioversion repeated along with amiodarone 600 mg QD for 4 weeks then 200 mg QD vs	MC, RCT Patients with recurrent persistent AF or atrial flutter, who have undergone one electrical cardioversion during the previous 2 years, with a maximum of 2	N=522 2 years	Primary: Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse effects of antiarrhythmic drugs Secondary: Not reported	Primary: The composite end point occurred in 44 (17.2%) patients in rate-control group and in 60 (22.6%) patients in the rhythm-control group (absolute difference of -5.4; 90% CI, -11.0 to 0.4). Death from cardiovascular causes occurred in 18 (7.0%) patients in rate-control group and in 18 (6.8%) patients in the rhythm-control group (absolute difference of 0.2; 90% CI, -3.4 to 3.9). Heart failure occurred in nine (3.5%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of -1.0; 90% CI, -3.8 to 1.8). Thromboembolic complications occurred in 14 (5.5%) patients in rate-control group and in 21 (7.9%) patients in the rhythm-control group (absolute difference of -2.4; 90% CI, -6.0 to 1.2). Bleeding occurred in 12 (4.7%) patients in rate-control group and in nine (3.4%) patients in the rhythm-control group (absolute difference of 1.3; 90% CI, -1.5 to 4.1). Severe adverse effects of antiarrhythmic drugs occurred in two (0.8%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of -3.7; 90% CI, -6.0 to -1.4). A pacemaker was implanted in three (1.2%) patients in rate-control group and in eight (3.0%) patients in the rhythm-control group (-1.8; 90% CI, -3.9 to 0.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rate control therapy: digitalis, non-dihydropyridine calcium channel blocker, and β-blocker, alone or in combination				Secondary: Not reported
Opolski et al.[47] (2004) HOT CAFÉ Rhythm control therapy: propafenone 450 to 600 mg QD, disopyramide 300 to 600 mg QD, or sotalol 160 to 320 mg QD vs rate control therapy: β-blockers, non-dihydropyridine calcium channel blockers, digoxin, or a combination of these drugs. All patients underwent electric cardioversion prior to the initiation of	MC, OL, RCT Patients between 50 to 75 years of age with AF known to be present continuously for between seven days and two years with acceptable etiology of the arrhythmia related to ischemic heart disease, arterial hypertension, hemodynamically insignificant valvular heart disease, or lack of assessable etiology	N=205 1 year	Primary: Composite of death from any cause (thromboembolic complications and intracranial or other major hemorrhage) Secondary: Rate control, sinus rhythm maintenance, discontinuation of therapy (proarrhythmic effects), hemorrhage, hospitalization, new or worsening CHF, or changes in exercise tolerance	Primary: There was not a significant difference in composite of death from any cause between the rate control group and the rhythm control group (OR, 1.98; 95% CI, 0.28 to 22.3; P>0.71). Secondary: The patients in the rhythm control group had a significantly lower mean heart rate (79.1±8.6 beats/min) in 24-hour Holter monitoring compared to the patients in the rate control group (85.8±7.5 beats/min; P<0.003). Four patients in the rhythm control group experienced proarrhythmic effects. Whether this lead to discontinuation of therapy was not mentioned. At the end of the study, 66 patients (63.5%) in the rhythm control arm were in sinus rhythm, with 27 of these patients successfully maintained with the first antiarrhythmic compound administered after the first cardioversion. There was not a statistical difference seen in bleeding complications between the rhythm control group (eight patients) and rate control group (five patients). A significantly lower number of hospitalizations were seen in the rate control arm compared to the rhythm control arm (12 vs 74%, respectively; P<0.001). Both the rhythm control group and rate control group had significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
study medication.				improvements in CHF class at some point during follow-up compared to baseline (P<0.001 and P<0.05, respectively). No difference in NYHA functional class between patients initially randomized to the two strategies was found at the end of the follow-up period. At the end of the study, both maximal workload and exercise duration were higher in the rhythm control arm compared to the rate control arm (P<0.001 and P<0.001, respectively).
Shelton et al.[48] (2009) CAFE´-II Rhythm control therapy: amiodarone therapy (200 mg TID for 1 month, followed by 200 mg BID for 1 month, followed by 200 mg/day thereafter) vs rate control therapy: digoxin and β-blockers Cardioversion was allowed if patients in the rhythm control group remained in AF despite amiodarone	MC, RCT Patients >18 years of age with persistent AF and chronic symptomatic heart failure (NYHA >Class II symptoms) with evidence of systolic dysfunction on echocardiography	N=61 1 year	Primary: QOL using the Medical Outcomes Study Short Form-36 version II questionnaire Secondary: Proportion of patients in sinus rhythm, scores on the MLWHF questionnaire, NTproBNP, 6MWT, severity of left ventricular systolic dysfunction	Primary: Patients assigned to rhythm control had a greater improvement in QOL over one year compared to rate control (P=0.020 for Medical Outcomes Study Short Form-36 version II as a whole; P=0.050 for mental functioning and P=0.029 for physical functioning subgroups). Secondary: At one year, target ventricular rate control was achieved in 90% of patients assigned to the rate control group. Digoxin and β-blocker use at one year was 84 and 90%, respectively. All patients in the rate control group were in AF at each and every follow-up visit. Sinus rhythm was restored in 20% of patients using amiodarone alone. Cardioversion restored sinus rhythm in 78% patients in whom it was attempted. Overall, 87% of patients were converted from AF to sinus rhythm at some time during the study. The prevalence of AF in the rhythm control group was 53% at four months, 30% at eight months, and 34% at one year. The difference in QOL using the MLWHF questionnaire was not significant in patients assigned to rhythm control vs rate control (P=0.140). The median NTproBNP concentrations at one year were 1,480 and 685 pg/mL for rate and rhythm groups, respectively. A greater reduction was seen for those in the rhythm control group compared to rate control (P=0.047). The mean change in distance walked at one year was 27 and five meters

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy.				for rate and rhythm control, respectively (P=0.342). Patients assigned to rhythm control had a greater improvement in left ventricular function over one year compared to patients assigned to rate control (P=0.014).
Lafuente-Lafuente et al.[49] (2009) Antiarrhythmic drugs (amiodarone, aprindine, azimilide, bidisomide, flecainide, disopyramide, dofetilide, dronedarone, quinidine, propafenone, sotalol) vs placebo, drugs for rate control (digoxin, calcium channel blockers, β-blockers) or no treatment	MA (45 trials) Adults >16 years of age who had AF of any type and duration and in whom sinus rhythm had been restored, spontaneously or by any therapeutic intervention	N=12,559 Variable duration	Primary: Mortality, embolic complications, adverse events Secondary: Use of anticoagulation, recurrence of AF	Primary: No deaths were reported with flecainide in the three trials. Quinidine showed a trend to increase mortality compared to controls (OR, 2.26; 95% CI, 0.93 to 5.45; P=0.07). This trend was significant if missing patients were counted as deaths (OR, 2.29; 95% CI, 1.05 to 5.01; P=0.04), and when class IA drugs (quinidine and disopyramide) were combined (OR, 2.39; 95% CI 1.03 to 5.59; P=0.04). The number NNH for class IA drugs was 109 patients treated for one year to have one excess death. Sotalol showed a trend to increased mortality (OR, 2.09; 95% CI, 0.97 to 4.49; P=0.06) compared to controls. This trend was significant if missing patients were counted as deaths (OR, 2.27; 95% CI, 1.36 to 3.77; P=0.002). Amiodarone was associated with a reduction in mortality compared to combined class I drugs (OR, 0.39; 95% CI, 0.19 to 0.79; NNT, 17). When compared to controls, amiodarone showed no significant difference in mortality. No other significant difference in mortality was detected, either vs control or between different antiarrhythmics. The analysis of cardiovascular mortality gave the same results as that of all-cause mortality. Only five of the 30 studies comparing antiarrhythmics with a control reported stroke outcomes. They reported six strokes in 650 patients in the control groups and 20 strokes in 1,755 patients treated with antiarrhythmics. Withdrawals due to adverse effects were more frequent with all drugs, except aprindine and dofetilide, compared to controls. Pooled events rates varied from 9 to 23% for withdrawals due to adverse effects. The mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				number of patients needed to treat for one year to have one excess withdrawal from treatment ranged from nine (quinidine) to 27 (amiodarone, propafenone, or sotalol). Quinidine caused more withdrawals than the other class I drugs (OR, 2.25; 95% CI 1.45 to 3.51; P=0.0003). Amiodarone produced significantly fewer withdrawals than other class I drugs combined (OR, 0.52; 95% CI, 0.34 to 0.81; P=0.004). All antiarrhythmics increased proarrhythmic effects, with the exception of amiodarone and propafenone. Pooled events rates varied from 1 to 7% for proarrhythmia. The NNH for proarrhythmia ranged between 17 (flecainide) and 119 (dofetilide). Amiodarone produced significantly less proarrhythmic events than other class I drugs combined (OR, 0.28; 95% CI, 0.13 to 0.59; P=0.0007). Secondary: All class IA, class IC and class III drugs significantly reduced the recurrence of AF. Pooled recurrence rates of AF at one year were 71 to 84% in controls and were reduced to 42% to 67% in patients treated with antiarrhythmics. The NNT for one year to avoid one recurrence of AF were three with amiodarone, four with flecainide, five with dofetilide and propafenone, eight with quinidine and sotalol and 10 with dronedarone. Amiodarone reduced recurrences of AF significantly more than combined class I drugs (OR, 0.31; 95% CI, 0.21 to 0.45; P<0.0001) and more than sotalol (OR, 0.43; 95% CI 0.29 to 0.64; P<0.0001). No other differences between antiarrhythmics were detected. Chronic anticoagulation with warfarin was mandatory in only three studies. The decision on anticoagulation was left to the judgment of the attending physician in the remaining studies.
Gillinov et al.[50] (2016) Rhythm control therapy: amiodarone with or without a rate-slowing agent	MC, RCT Patients with new-onset postoperative AF in hemodynamically stable condition who were	N=523 60 days	Primary: Total number of days of hospitalization (including emergency department visits) within 60 days	Primary: The total numbers of hospital days in the rate-control group and the rhythm-control group were similar (median, 5.1 days and 5.0 days, respectively; P=0.76). Secondary: The mean length of stay for the index hospitalization after randomization was 5.5 days in the rate-control group and 5.8 days in the rhythm-control

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rate control therapy: "medications to slow the heart rate"	undergoing elective cardiac surgery to treat coronary artery disease or heart-valve disease; none of the patients had a history of AF		after randomization Secondary: Duration of the hospital stay from randomization to the time of eligibility for discharge on the basis of criteria regarding AF, the length of the index hospitalization, the need for readmission, heart rhythm and time to conversion to a sustained stable rhythm without AF, the need for permanent placement of a pacemaker, and the rates of death and adverse events	group (median, 4.3 in each group; P=0.88). A sensitivity analysis to determine the influence of treatment nonadherence confirmed the results of the intention-to-treat analysis (P=0.51 for the total hospital stay, P=0.72 for the index hospital stay). During the study period, there were 159 hospital readmissions, including emergency department visits, with no significant between-group difference in the rate per 100 patient-months. The proportion of patients who were readmitted within 30 days after hospital discharge was 22.8% in the rate-control group and 21.4% in the rhythm-control group (P=0.71). A total of 89.9% of the patients in the rate-control group and 93.5% of those in the rhythm-control group had a stable, sustained heart rhythm without atrial fibrillation at hospital discharge (P=0.14). At 60 days, five patients had died: three in the rate-control group and two in the rhythm-control group (P=0.64). There were no significant differences in the overall rates of serious adverse events between the rate-control group and the rhythm-control group (24.8 per 100 patient-months and 26.4 per 100 patient-months, respectively; P=0.61)

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, SB=single-blinded
Miscellaneous abbreviations: 6MWT=6-minute corridor walk test, AD=arrhythmic death, AF=atrial fibrillation, AT=atrial tachyarrhythmias, CABG=coronary artery bypass graft, CHF=congestive heart failure, CI=confidence interval, ECG=electrocardiographic, HR=hazard ratio, LVEF=left ventricular ejection fraction, MI=myocardial infarction, MLWHF=Minnesota Living with Heart Failure, MUGA=multiple-gated nuclear angiography, NNH=number needed to harm, NNT=number needed to treat, NTproBNP=N-terminal prohormone of brain natriuretic peptide, NYHA=New York Heart Association, OR=odd ratio, QOL=quality of life, RR=relative risk, RVF=resuscitated ventricular fibrillation, SF-12=12-Item Short Form Health Survey, SND=sinus node disease, TIA=transient ischemic attack, VDPs=ventricular premature depolarizations, VT=ventricular tachycardia

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 17. Relative Cost of the Antiarrhythmic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amiodarone	injection, tablet	Nexterone®, Pacerone®*	$	$
Disopyramide	capsule, extended-release capsule	Norpace®*, Norpace CR®	$$$$$	$$$$
Dofetilide	capsule	Tikosyn®*	$$$$$	$$$
Dronedarone	tablet	Multaq®	$$$$$	N/A
Flecainide	tablet	N/A	N/A	$
Mexiletine	capsule	N/A	N/A	$$
Propafenone	extended-release capsule, tablet	Rythmol SR®*	$$$$$	$
Quinidine	extended-release tablet, tablet	N/A	N/A	$$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The antiarrhythmic agents are effective for the treatment of atrial fibrillation/flutter and ventricular arrhythmias. These agents differ with regards to their Food and Drug Administration (FDA)-approved indications, mechanism of action, pharmacokinetic properties, drug interactions, and adverse events. All of the antiarrhythmic agents are available in a generic formulation, with the exception of dronedarone.

There are several guidelines that provide recommendations on the use of antiarrhythmic agents for the treatment of both atrial and ventricular arrhythmias. The antiarrhythmics are generally not recommended as first-line agents for the treatment of ventricular arrhythmias. Amiodarone and sotalol may be used to treat ventricular tachycardias in patients with left ventricular dysfunction due to a prior myocardial infarction (MI) and who are not responding to β-blockade from other agents. In those patients with atrial fibrillation (AF), rate control is the recommended treatment strategy but rhythm control may be appropriate in certain circumstances, particularly in patients whose quality of life is affected by AF. Some antiarrhythmic agents may be appropriate to use for rhythm control in patients with particular disease states, for instance sotalol and Class IA antiarrhythmics may be used for postoperative AF or atrial flutter in patients with coronary artery disease without congestive heart failure.[3-7] Overall, the AFFIRM, RACE, and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies.[4,45-47] There are many factors that should be addressed prior to the selection of an antiarrhythmic agent for a patient, including the type of arrhythmia, concurrent disease states, and potential risk to benefit ratio of therapy. These agents have not been shown to improve mortality in patients with atrial or ventricular arrhythmias.[3-7]

Amiodarone is an effective treatment option for AF; however, its use is limited by toxicity (pulmonary, thyroid, and gastrointestinal), photosensitivity reactions, and bluish discoloration of the skin. Amiodarone is associated with a low risk of proarrhythmia in patients with left ventricular hypertrophy, heart failure, coronary artery disease, and previous MI.[14-17] Trials also support the efficacy of dofetilide for the prevention of atrial fibrillation/flutter. To reduce the risk of early proarrhythmia, dofetilide must be initiated in the hospital. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.[13-15]

Dronedarone is a non-iodinated analog of amiodarone, and as a result, it is less lipophilic and has a shorter half-life than amiodarone. These structural changes were made to reduce the risk of thyroid and pulmonary toxicity. Clinical trials have shown that dronedarone reduces the risk of recurrent atrial fibrillation/flutter and is effective for the long-term maintenance of sinus rhythm.[27,28,34] However, the ANDROMEDA trial was terminated early due to an excess number of deaths in patients with heart failure who received dronedarone. Death from any cause occurred in 8.1% of patients receiving dronedarone and 3.8% of patients receiving placebo (hazard ratio, 2.13; 95% confidence interval, 1.07 to 4.25; P=0.03).[32] As a result, dronedarone is contraindicated in patients with New York Heart Association (NYHA) class IV heart failure or NYHA class II to III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.[8] In a comparative study, dronedarone was found to be less effective than amiodarone for the composite end point of AF recurrence or premature drug discontinuation for intolerance or lack of efficacy. There were fewer thyroid and neurological adverse events with dronedarone, as well as fewer patients discontinuing therapy due to adverse events compared to amiodarone.[38,51] There were no studies found in the medical literature which evaluated the use of dronedarone for the prevention or treatment of ventricular arrhythmias. In December 2011, the FDA released a safety warning regarding an increased risk of death or serious cardiovascular events with dronedarone. A completed safety review, which included data from the PALLAS and ATHENA trials, demonstrated that dronedarone increased the risk of serious cardiovascular events, including death, when used by patients in permanent AF. Based on the findings of the FDA safety review, the approved package labeling changed to include additional recommendations for the use of dronedarone in patients with non-permanent AF.[52]

There is insufficient evidence to support that one brand antiarrhythmic agent is 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 antiarrhythmic agents 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 antiarrhythmic agent 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cardiotonic Agents
AHFS Class 240408
February 7, 2024

I. Overview

Digoxin is the only cardiotonic agent that is currently available. It inhibits sodium-potassium ATPase, which increases the intracellular concentration of sodium and calcium. This leads to an increase in the force/velocity of myocardial contractions, decreased activation of the sympathetic nervous system and renin-angiotensin system, and a decrease in heart rate and conduction velocity through the atrioventricular node. Digoxin is an effective treatment for heart failure due to its positive inotropic and neurohormonal deactivating effects. It is also beneficial for atrial arrhythmias due to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system, which may lead to toxicity.[1-3]

The cardiotonic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Digoxin injection, solution, and tablets are all available in a generic formulation. This class was last reviewed in February 2022.

Table 1. Cardiotonic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Digoxin	injection, solution, tablet	Lanoxin®*, Lanoxin Pediatric®	digoxin

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Cardiotonic Agents

Clinical Guideline	Recommendation(s)
American Heart Association/ American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation (2014)[4]**	Recommendations for risk-based antithrombotic therapy: Class I • In patients with atrial fibrillation (AF), antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences (Level of Evidence: C). • Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent (Level of Evidence: B). • In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence: B). • For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) should be based on type and location of the prosthesis (Level of Evidence: B). • For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran, rivaroxaban, or apixaban (Level of Evidence: B). • For patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (Level of Evidence: A) • For patients with nonvalvular AF unable to maintain a therapeutic INR level with

Clinical Guideline	Recommendation(s)
	warfarin, use of a direct thrombin or factor Xa inhibitor is recommended (Level of Evidence: C). • Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks (Level of Evidence: C). • Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding (Level of Evidence: C). • For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated (Level of Evidence: C). • Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (Level of Evidence: B). • For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF (Level of Evidence: C). Class IIa • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Level of Evidence: B). • For patients with nonvalvular AF with a CHA_2DS_2-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (Level of Evidence: B). Class IIb • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence: C). • For patients with nonvalvular AF and moderate-to-severe chronic kidney disease with a CHA_2DS_2-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established (Level of Evidence: C). • In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture (Level of Evidence: C). • Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B). Class III: No Benefit • The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (Level of Evidence: C). Class III: Harm • The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (Level of Evidence: B). <u>Recommendations for rate control:</u> Class I • Control of the ventricular rate using a beta blocker or nondihydropyridine (non-DHP) calcium channel blocker (CCB) is recommended for patients with

Clinical Guideline	Recommendation(s)
	paroxysmal, persistent, or permanent AF (Level of Evidence: B). • Intravenous administration of a beta blocker or non-DHP CCB is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Level of Evidence: B). • In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range (Level of Evidence: C). Class IIa • A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF (Level of Evidence: B). • Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (Level of Evidence: B). • Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (Level of Evidence: B). Class IIb • A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and left ventricular systolic function is preserved (Level of Evidence: B). • Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated (Level of Evidence: C). Class III: Harm • AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications (Level of Evidence: C). • Non-DHP CCBs should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise (Level of Evidence: C). • In patients with pre-excitation and AF, digoxin, non-DHP CCBs, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation. (Level of Evidence: B). • Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death (Level of Evidence: B). <u>Recommendations for Thromboembolism Prevention</u>: Class I • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method used to restore sinus rhythm (Level of Evidence: B). • For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated (Level of Evidence: C). • For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy (Level of Evidence: C). • Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile

Clinical Guideline	Recommendation(s)
	(Level of Evidence: C). Class IIa • For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks (Level of Evidence: B). • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion (Level of Evidence: C). Class IIb • For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation (Level of Evidence: C). <u>Recommendations for pharmacological cardioversion</u> Class I • Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Level of Evidence: A). Class IIa • Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF (Level of Evidence: A). • Propafenone or flecainide ("pill-in-the-pocket") in addition to a beta blocker or non-DHP CCB is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (Level of Evidence: B). Class III: Harm • Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes (Level of Evidence: B). <u>Recommendations for antiarrhythmic drugs to maintain sinus rhythm</u> Class I • Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended (Level of Evidence: C). • The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Level of Evidence: A): o Amiodarone o Dofetilide o Dronedarone o Flecainide o Propafenone o Sotalol • The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug (Level of Evidence: C). • Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated (Level of Evidence: C). Class IIa

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	• A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy (Level of Evidence: C). Class IIb • It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF (Level of Evidence: C). Class III: Harm • Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent (Level of Evidence: C), including dronedarone (Level of Evidence: B). • Dronedarone should not be used for treatment of AF in patients with New York Heart Association class III and IV HF or patients who have had an episode of decompensated HF in the past four weeks. (Level of Evidence: B). <u>Upstream therapy</u> Class IIa • An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF with reduced left ventricular ejection fraction (Level of Evidence: B). Class IIb • Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (Level of Evidence: B). • Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (Level of Evidence: A). Class III: No Benefit • Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (Level of Evidence: B).

American Heart Association/American College of Cardiology/ Heart Rhythm Society: **2019 Focused Update of the 2014 Guideline for the Management of Patients with Atrial Fibrillation (2019)[5]**	<u>Recommendations for selecting an anticoagulant regimen</u>
	• For patients with atrial fibrillation (AF) and an elevated CHA_2DS_2-VASc score of two or greater in men or three or greater in women, oral anticoagulants are recommended. Options include:
	  ○ Warfarin
	  ○ Dabigatran
	  ○ Rivaroxaban
	  ○ Apixaban
	  ○ Edoxaban
	• Non–vitamin K oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve)
	• Among patients treated with warfarin, the international normalized ratio (INR) should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable.
	• In patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), the CHA_2DS_2-VASc score is recommended for assessment of stroke risk.
	• For patients with AF who have mechanical heart valves, warfarin is recommended.
	• Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.
	• Renal function and hepatic function should be evaluated before initiation of a NOAC and should be reevaluated at least annually.

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	• In patients with AF, anticoagulant therapy should be individualized on the basis of shared decision-making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient's values and preferences. • For patients with atrial flutter, anticoagulant therapy is recommended according to the same risk profile used for AF. • Reevaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risks. • For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended. • For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy. • For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation. • For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD (serum creatinine ≥1.5 mg/dL [apixaban], CrCl 15 to 30 mL/min [dabigatran], CrCl <50 mL/min [rivaroxaban], or CrCl 15 to 50 mL/min [edoxaban]) with an elevated CHA_2DS_2-VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, apixaban, or edoxaban). • For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered. • In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk. • The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve. <u>Interruption and bridging anticoagulation</u> • Bridging therapy with unfractionated heparin or low-molecular-weight heparin is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding. • For patients with AF without mechanical heart valves who require interruption of warfarin for procedures, decisions about bridging therapy (unfractionated heparin or low-molecular-weight heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated. • Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure. • Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding. <u>Rhythm control: recommendations for prevention of thromboembolism</u> • For patients with AF or atrial flutter of 48 hours' duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0), a factor Xa inhibitor, or direct thrombin inhibitor is recommended for at least three weeks before and at least four weeks after cardioversion, regardless of the

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	CHA_2DS_2-VASc score or the method (electrical or pharmacological) used to restore sinus rhythm. • For patients with AF or atrial flutter of more than 48 hours' duration or unknown duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated. • After cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile and bleeding risk profile. • For patients with AF or atrial flutter of less than 48 hours' duration with a CHA_2DS_2-VASc score of 2 or greater in men and 3 or greater in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor is reasonable as soon as possible before cardioversion, followed by long-term anticoagulation therapy. • For patients with AF or atrial flutter of 48 hours' duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform transesophageal echocardiography before cardioversion and proceed with cardioversion if no left atrial thrombus is identified, including in the LAA, provided that anticoagulation is achieved before transesophageal echocardiography and maintained after cardioversion for at least four weeks. • For patients with AF or atrial flutter of less than 48 hours' duration with a CHA_2DS_2-VASc score of 0 in men or 1 in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor, versus no anticoagulant therapy, may be considered before cardioversion, without the need for postcardioversion oral anticoagulation. <u>Recommendations for AF complicating acute coronary syndrome (ACS)</u> • For patients with ACS and AF at increased risk of systemic thromboembolism (based on CHA_2DS_2-VASc risk score of 2 or greater), anticoagulation is recommended unless the bleeding risk exceeds the expected benefit. • Urgent direct-current cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control. • Intravenous beta blockers are recommended to slow a rapid ventricular response to AF in patients with ACS who do not display HF, hemodynamic instability, or bronchospasm. • If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone percutaneous coronary intervention (PCI) with stenting for ACS, it is reasonable to choose clopidogrel in preference to prasugrel. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist is reasonable to reduce the risk of bleeding as compared with triple therapy. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with $P2Y_{12}$ inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily is reasonable to reduce the risk of bleeding as compared with triple therapy. • In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with triple therapy.

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	• If triple therapy (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF who are at increased risk of stroke (based on CHA_2DS_2-VASc risk score of 2 or greater) and who have undergone PCI with stenting (drug eluting or bare metal) for ACS, a transition to double therapy (oral anticoagulant and $P2Y_{12}$ inhibitor) at four to six weeks may be considered. • Administration of amiodarone or digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability. • Administration of nondihydropyridine calcium antagonists may be considered to slow a rapid ventricular response in patients with ACS and AF only in the absence of significant HF or hemodynamic instability.
American Association for Thoracic Surgery: **2014 AATS Guidelines for the Prevention and Management of Peri-Operative Atrial Fibrillation and Flutter (POAF) for Thoracic Surgical Procedures (2014)[6]**	<u>Recommended prevention strategies for all postoperative atrial fibrillation (POAF) patients</u> • Patients taking β-blockers prior to thoracic surgery should continue them in the postoperative period to avoid β-blockade withdrawal. • Intravenous magnesium supplementation may be considered to prevent postoperative AF when serum magnesium level is low or it is suspected that total body magnesium is depleted. • Digoxin should not be used for prophylaxis against AF. <u>Recommended prevention strategies for intermediate to high-risk POAF patients</u> • It is reasonable to administer diltiazem to those patients with preserved cardiac function who are not taking β-blockers preoperatively in order to prevent POAF. • It is reasonable to consider the postoperative administration of amiodarone to reduce the incidence of POAF for intermediate and high risk patients undergoing pulmonary resection. • Postoperative administration of intravenous amiodarone may be considered to prevent POAF in patients undergoing esophagectomy. • Atorvastatin may be considered to prevent POAF for statin naïve patients scheduled for intermediate and high risk thoracic surgical procedures. <u>Rate control recommendations for patients with new onset POAF</u> • Intravenous administration of beta-blockers (e.g., esmolol or metoprolol) or nondihydropyridine calcium channel blockers (diltiazem or verapamil) is recommended to achieve rate control (heart rate ≤110 bpm) for patients who develop POAF with rapid ventricular response. • Caution should be used with patients with hypotension, left ventricular (LV) dysfunction, or heart failure. • Combination use of atrioventricular (AV) nodal blocking agents, such as beta-blockers (e.g., esmolol or metoprolol), nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, can be useful to control heart rates when a single agent fails to control rates of POAF. The choice should be individualized and doses modified to avoid bradycardia. • For patients with hypotension, heart failure or LV dysfunction, or when other measures are unsuccessful or contraindicated, intravenous amiodarone can be useful for control of heart rate. Amiodarone could result in conversion to sinus rhythm, and if it is initiated after 48 hours of AF, both a transesophageal echocardiography (TEE) when possible, to rule out left atrial/LA appendage (LA/LAA) thrombus, and full anticoagulation should be considered. • For patients with heart failure, LV dysfunction or hypotension, intravenous digoxin may be considered for rate control of POAF. • For patients with ventricular preexcitation (i.e., Wolff-Parkinson-White syndrome) and POAF, use of AV nodal blocking agents, such as beta-blockers (e.g., esmolol or metoprolol), intravenous amiodarone, nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, should be

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	avoided. <u>Recommendations for the use of antiarrhythmic drugs for pharmacologic cardioversion of POAF</u> • Restoration of sinus rhythm with pharmacologic cardioversion is reasonable in patients with symptomatic, hemodynamically stable POAF. Intravenous amiodarone can be useful for pharmacologic cardioversion of POAF. • It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm for patients with recurrent or refractory POAF. • Amiodarone, sotalol, flecainide, propafenone, or dofetilide can be useful to maintain sinus rhythm in patients with POAF, depending on underlying heart disease, renal status and other comorbidities. • Flecainide or propafenone may be considered for pharmacologic cardioversion of POAF and maintenance of sinus rhythm if the patient has had no prior history of myocardial infarction, coronary artery disease, impaired LV function, significant LV hypertrophy, or valvular heart disease that is considered moderate or greater. These agents may need to be combined with an AV nodal blocking agent. • Intravenous ibutilide or procainamide may be considered for pharmacologic conversion of POAF for patients with structural heart disease and new onset POAF, but no hypotension or manifestations of congestive heart failure. Serum electrolytes and QTc interval must be within a normal range and patients must be closely monitored during and for at least six hours after the infusion if either ibutilide or procainamide. • Intravenous ibutilide or procainamide may be considered for patients with POAF and an accessory pathway. • Flecainide and propafenone should not be used to treat POAF in patients with a history of a prior myocardial infarction, coronary artery disease, and/or severe structural heart disease, including severe left ventricular hypertrophy, or significantly reduced left ventricular ejection fraction. • Dronedarone should not be used for treatment of POAF in patients with heart failure. <u>Recommendations for prevention of thromboembolism for patients with stable atrial fibrillation/flutter undergoing direct current cardioversion</u> • For stable patients with POAF of 48-hours duration or longer, anticoagulation (with warfarin for INR 2.0 to 3.0, a novel oral anti-coagulant [NOAC] or LMWH) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the method (electrical or pharmacological) used to restore sinus rhythm. • During the first 48 hours after the onset of POAF, the need for anticoagulation before and after direct current (DC) cardioversion may be based on the patient's risk of thromboembolism (CHA_2DS_2-VASc score) balanced by the risk of postoperative bleeding. • For POAF lasting longer than 48 hours, as an alternative to three weeks of therapeutic anticoagulation prior to cardioversion of POAF, it is reasonable to perform TEE in search of thrombus in the LA or LA appendage, preferably with full anticoagulation at the time of TEE in anticipation of DC cardioversion after the TEE. • For POAF lasting longer than 48 hours in patients who are not candidates for TEE (e.g., post-esophageal surgery), an initial rate control strategy combined with therapeutic anticoagulation using warfarin (aiming for INR 2.0 to 3.0), a direct thrombin inhibitor (e.g. dabigatran), factor Xa inhibitor (e.g. rivaroxaban, apixaban), or LMWH is recommended for at least three weeks prior to and four weeks after cardioversion. • Anticoagulation recommendations for cardioversion of atrial flutter are similar to

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	those for atrial fibrillation. • For patients with an identified thrombus, cardioversion should not be performed until a longer period of anticoagulation is achieved (usually at least three weeks) and in accordance with established AF guidelines. Management of anticoagulation for new onset POAF • For the prevention of strokes for patients who develop POAF lasting longer than 48 hours, it is recommended to administer antithrombotic medications similarly to non-surgical patients. Anticoagulation within the first 48-hours of POAF should be considered based on the CHA_2DS_2-VASc risk score of the patient for stroke weighed against the risk of postoperative bleeding. • New oral anticoagulants (dabigatran, rivaroxaban, apixaban) are reasonable as an alternative to warfarin for patients who do not have a prosthetic heart valve, hemodynamically significant valve disease, and/or severe renal impairment or risk of GI bleeding. • It is reasonable to continue anticoagulation therapy for four weeks after the return of sinus rhythm because of the possibility of slowly resolving impairment of atrial contraction with an associated ongoing risk for thrombus formation and for delayed embolic events. • New oral anticoagulants should be avoided for patients at risk for serious bleeding (including GI bleeding) as they cannot be readily reversed. However, their use may be recommended in situations where achievement of a therapeutic INR with warfarin has proved to be difficult.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)**[7]	Treatment of Stage A heart failure (HF) • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) Treatment of Stage B heart failure • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they

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	increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce

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	mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B)

Clinical Guideline	Recommendation(s)
	Treatment of Stage D (advanced/refractory) HF • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B) Treatment of Transthyretin Cardiac Amyloidosis • In select patients with wild-type or variant trans-thyretin cardiac amyloidosis and NYHA class I to III HF symptoms, transthyretin tetramer sta-bilizer therapy (tafamidis) is indicated to reduce cardiovascular morbidity and mortality. • At 2020 list prices, tafamidis provides low economic value (>$180 000 per QALY gained) in patients with HF with wild-type or variant transthyretin cardiac amyloidosis. • In patients with cardiac amyloidosis and AF, anticoagulation is reasonable to reduce the risk of stroke regardless of the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category) score.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[8]	Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker. Patients should also receive an ACE

Clinical Guideline	Recommendation(s)
	inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a beta-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a beta-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.

Clinical Guideline	Recommendation(s)
	• SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk • of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.

National Institute for Health and Clinical Excellence: **Chronic heart failure in adults: management (2018)[9]**	<u>Treating heart failure with reduced ejection fraction</u>
	• First-line treatment
	  o Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have heart failure with reduced ejection fraction.
	• ACE inhibitors
	  o Do not offer ACE inhibitor therapy if there is a clinical suspicion of hemodynamically significant valve disease until the valve disease has been assessed by a specialist.
	  o Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every two weeks) until the target or maximum tolerated dose is reached.
	  o Measure serum sodium and potassium, and assess renal function, before and one to two weeks after starting an ACE inhibitor, and after each dose increment.
	  o Measure blood pressure before and after each dose increment of an ACE inhibitor.
	  o Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell.
	• Alternative treatments if ACE inhibitors are not tolerated
	  o Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side effects with ACE inhibitors.
	  o Measure serum sodium and potassium, and assess renal function, before and

Clinical Guideline	Recommendation(s)
	after starting an ARB and after each dose increment. o Measure blood pressure after each dose increment of an ARB. o Once the target or maximum tolerated dose of an ARB is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell. o If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have heart failure with reduced ejection fraction. • Beta-blockers o Do not withhold treatment with a beta-blocker solely because of age or the presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. o Introduce beta-blockers in a 'start low, go slow' manner. Assess heart rate and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. o Switch people whose condition is stable and who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. • Mineralocorticoid receptor antagonists (MRAs) o Offer an MRA, in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. o Measure serum sodium and potassium, and assess renal function, before and after starting an MRA and after each dose increment. o Measure blood pressure before and after each dose increment of an MRA. o Once the target, or maximum tolerated, dose of an MRA is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell. • Specialist treatment o Ivabradine is recommended as an option for treating chronic heart failure for people: ▪ with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and ▪ who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and ▪ who are given ivabradine in combination with standard therapy including beta-blocker therapy, ACE inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and ▪ with a left ventricular ejection fraction of 35% or less. o Ivabradine should only be initiated after a stabilization period of four weeks on optimized standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. o Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. o Sacubitril-valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: ▪ with New York Heart Association (NYHA) class II to IV symptoms and ▪ with a left ventricular ejection fraction of 35% or less and ▪ who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or ARBs. o Treatment with sacubitril-valsartan should be started by a heart failure

Clinical Guideline	Recommendation(s)
	specialist with access to a multidisciplinary heart failure team. o Hydralazine in combination with nitrate ▪ Seek specialist advice and consider offering hydralazine in combination with nitrate (especially if the person is of African or Caribbean family origin and has moderate to severe heart failure [NYHA class III/IV] with reduced ejection fraction). o Digoxin ▪ Digoxin is recommended for worsening or severe heart failure with reduced ejection fraction despite first-line treatment for heart failure. Seek specialist advice before initiating. ▪ Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within eight to 12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence. ▪ The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. <u>Treating heart failure with reduced ejection fraction in people with chronic kidney disease</u> • For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR of 30 ml/min/1.73 m^2 or above: o offer the treatment outlined above and o if the person's eGFR is 45 ml/min/1.73 m^2 or below, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, MRAs and digoxin. • For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR below 30 ml/min/1.73 m^2, the specialist heart failure multidisciplinary team should consider liaising with a renal physician. • Monitor the response to titration of medicines closely in people who have heart failure with reduced ejection fraction and chronic kidney disease, taking into account the increased risk of hyperkalemia. <u>Managing all types of heart failure: Pharmacological treatment</u> • Diuretics o Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. o People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice. • Calcium-channel blockers o Avoid verapamil, diltiazem and short-acting dihydropyridine agents in people who have heart failure with reduced ejection fraction. • Amiodarone o Make the decision to prescribe amiodarone in consultation with a specialist. o Review the need to continue the amiodarone prescription at the six-monthly clinical review. o Offer people taking amiodarone liver and thyroid function tests, and a review of side effects, as part of their routine 6-monthly clinical review. • Anticoagulants o For people who have heart failure and atrial fibrillation, follow the recommendations on anticoagulation in the NICE guideline on atrial fibrillation. Be aware of the effects of impaired renal and liver function on

Clinical Guideline	Recommendation(s)
	anticoagulant therapies. ○ In people with heart failure in sinus rhythm, anticoagulation should be considered for those with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus. • Vaccinations ○ Offer people with heart failure an annual vaccination against influenza. ○ Offer people with heart failure vaccination against pneumococcal disease (only required once). • Contraception and pregnancy ○ In women of childbearing potential who have heart failure, contraception and pregnancy should be discussed. If pregnancy is being considered or occurs, specialist advice should be sought. Subsequently, specialist care should be shared between the cardiologist and obstetrician.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cardiotonic agents 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 Cardiotonic Agents[1-2]

Indication	Digoxin
Control of ventricular response rate in adult patients with chronic atrial fibrillation	✔
Increase myocardial contractility in pediatric patients with heart failure	✔
Treatment of mild to moderate heart failure in adults	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the cardiotonic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cardiotonic Agents[10]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (days)
Digoxin	60 to 85 (tablet) 70 to 85 (oral solution)	25	Liver (13)	Renal (50 to 70) Bile (6 to 8) Feces (3 to 5)	1.5 to 2.0

V. Drug Interactions

Major drug interactions with the cardiotonic agents are listed in Table 5.

Table 5. Major Drug Interactions with the Cardiotonic Agents[10]

Generic Name(s)	Interaction	Mechanism
Digoxin	Acarbose	Pharmacologic effects and plasma concentrations of digoxin may be decreased by acarbose. The mechanism of this interaction is unknown.
Digoxin	Activated charcoal	Charcoal can reduce gastrointestinal absorption of many drugs and actually remove drugs from the systemic circulation which will

Generic Name(s)	Interaction	Mechanism
		reduce the effectiveness or toxicity of a given agent.
Digoxin	Antineoplastic agents	Drug-induced alterations of the intestinal mucosa may be involved in reduced gastrointestinal absorption of digoxin; therefore, serum levels of digoxin may be reduced and actions may be decreased.
Digoxin	Amifampridine	Concurrent use of amifampridine and drugs with narrow therapeutic window may result in increased or decreased exposure of drugs with a narrow therapeutic index.
Digoxin	Aminoglycosides	The mechanism of this interaction is unknown. The rate and extent of digoxin absorption may be reduced, which could reduce the pharmacologic effect of the drug.
Digoxin	Amiodarone	Serum digoxin levels may be increased, resulting in an increase in the pharmacologic and toxic effects of digoxin. Mechanism of interaction is unknown.
Digoxin	β-blockers	Carvedilol may increase digoxin bioavailability. Possible additive depression of myocardial conduction and decreased renal tubular digoxin secretion may occur. Serum digoxin concentrations may be increased by coadministration of carvedilol. Synergistic bradycardia may occur in some patients.
Digoxin	Cholestyramine	Bioavailability and pharmacologic effects of digoxin may be decreased by bile acid sequestrants. The gastrointestinal absorption of digoxin may be decreased due to formation of a physical or chemical complex with bile acid sequestrants.
Digoxin	Colestipol	Colestipol may physically bind with digoxin and cause a decrease in its gastrointestinal absorption and normal enterohepatic recycling. Colestipol may decrease the half-life of digoxin, possibly reducing its therapeutic effect.
Digoxin	Cyclosporine	Mechanism of interaction unknown. The pharmacologic effects of digoxin may be increased, possibly leading to toxicity.
Digoxin	Diltiazem	Pharmacologic effects of digoxin may be increased by diltiazem. Elevated digoxin serum concentrations and toxicity, characterized by gastrointestinal and neuropsychiatric symptoms and cardiac arrhythmias, may occur. Pharmacodynamic effects of diltiazem and digoxin may be additive. The clearance of digoxin may be decreased by diltiazem.
Digoxin	Dronedarone	Plasma concentrations and pharmacologic effects of digoxin may be increased due to inhibition of P-glycoprotein (P-gp) efflux transport by dronedarone. Digoxin may also enhance the electrophysiologic effects of dronedarone.
Digoxin	Indomethacin	Serum concentrations and pharmacologic effects of digoxin may be increased by indomethacin. By decreasing renal blood flow, indomethacin may decrease renal elimination of digoxin.
Digoxin	Itraconazole	Itraconazole may increase pharmacologic effects and plasma concentrations of digoxin by decreasing renal the renal excretion of digoxin; toxicity may occur.
Digoxin	Loop diuretics	Increased urinary excretion of potassium and magnesium affecting cardiac muscle action, and other factors may also be involved. Diuretic-induced electrolyte disturbances may predispose patients to digoxin-induced arrhythmias.
Digoxin	Macrolides and ketolides	Macrolides and ketolides may increase serum concentrations and toxic effects of digoxin. Inhibition of the P-glycoprotein transport system by macrolides and ketolides may increase the oral absorption and reduce the renal secretion of digoxin. Macrolides and ketolides-related alterations in gut flora may also play a role.
Digoxin	Metoclopramide	By increasing gastrointestinal motility, metoclopramide may decrease the plasma levels of digoxin, decreasing therapeutic

Generic Name(s)	Interaction	Mechanism
		effects. This interaction may not occur with high-bioavailability digoxin formulations.
Digoxin	Paroxetine	Inhibition of renal tubular P-glycoprotein excretion of digoxin by paroxetine is suspected, increasing digoxin serum concentrations, increasing the pharmacologic and toxic effects.
Digoxin	Penicillamine	Pharmacologic effects of digoxin may be decreased. Reduced digoxin serum levels, possibly with a suboptimal therapeutic response may result. The mechanism of this interaction is unknown.
Digoxin	Protease inhibitors	Protease inhibitors may increase plasma concentrations and pharmacologic effects of digoxin. Although the exact mechanism is unknown, P-glycoprotein inhibition by protease inhibitors may enhance the absorption and decrease the renal excretion of digoxin.
Digoxin	Propafenone	Actual mechanism of the interaction is unknown. The volume of distribution of digoxin may be decreased along with a decrease in the renal and non-renal clearance which may increase serum digoxin levels, resulting in toxicity.
Digoxin	Quinidine	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.
Digoxin	Quinine	Quinine may increase digoxin serum concentrations. Toxicity characterized by gastrointestinal and neuromuscular symptoms and cardiac arrhythmias may occur.
Digoxin	Spironolactone	Spironolactone may attenuate the positive inotropic effect of digoxin. Serum levels of digoxin also may be increased. Additionally, spironolactone may interfere with the digoxin radioimmunoassay, resulting in falsely elevated digoxin levels.
Digoxin	Tetracyclines	Tetracycline may reverse the process by which digoxin is metabolized by gastrointestinal flora by altering gastrointestinal flora, allowing for more digoxin to be absorbed and increasing digoxin serum levels.
Digoxin	Thiazide diuretics	Increased urinary excretion of potassium and magnesium affecting cardiac muscle, and other factors may be involved. Thiazide-induced electrolyte disturbances may predispose to digoxin-induced arrhythmias.
Digoxin	Thioamines	Thioamines may alter pharmacologic effects and plasma concentrations of digoxin. The mechanism of this interaction is unknown.
Digoxin	Thyroid hormones	The therapeutic effectiveness of digoxin may be decreased, with possible exacerbation of cardiac arrhythmias or congestive heart failure. The mechanism of this interaction is unknown.
Digoxin	Verapamil	Verapamil may alter the pharmacokinetics and increase serum concentrations of digoxin. Toxicity characterized by gastrointestinal symptoms, neuropsychiatric symptoms, and cardiac arrhythmias may result.

VI. Adverse Drug Events

The most common adverse drug events reported with the cardiotonic agents are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Cardiotonic Agents[3]

Adverse Events	Digoxin
Cardiovascular	
Cardiac dysrhythmia	✔

Adverse Events	Digoxin
Heart arrest	✔
Palpitation	✔
Tachycardia	✔
Ventricular extrasystole	✔
Central Nervous System	
Apathy	✔
Confusion	✔
Dizziness	✔
Headache	✔
Mental disturbances	✔
Weakness	✔
Gastrointestinal	
Abdominal pain	✔
Anorexia	✔
Diarrhea	✔
Hemorrhagic necrosis of the intestines	✔
Intestinal ischemia	✔
Nausea	✔
Vomiting	✔
Other	
Death	✔
Gynecomastia	✔
Macropapular rash	✔
Other skin reactions	✔
Thrombocytopenia	✔

✔ Percent not specified.

VII. Dosing and Administration

The usual dosing regimens for the cardiotonic agents are listed in Table 7. Several factors must be taken into account when dosing digoxin, including the patient's lean body weight, renal function, age, concomitant disease states, concurrent medications, and other factors that may alter the pharmacokinetic properties of digoxin.[4-5]

Table 7. Usual Dosing Regimens for the Cardiotonic Agents[1-3,10]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Digoxin	Control of ventricular response rate in patients with chronic atrial fibrillation: Injection: doses should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects Solution, tablet: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose (10 to 15 µg/kg) followed by maintenance dosing (3.4 to 5.1 µg/kg/day) if rapid titration is desired OR initiated with maintenance dosing (3.4 to 5.1 µg/kg/day) without a	Increase myocardial contractility in pediatric patients with heart failure in children >10 years of age: Injection: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose followed by maintenance dosing if rapid titration is desired OR initiated with maintenance dosing without a loading dose Solution, tablet: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can	Injection*: 100 µg/mL 250 µg/mL Solution: 50 µg/mL Tablet: 62.5 µg 125 µg 250 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	loading dose <u>Treatment of mild to moderate heart failure:</u> Injection: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose followed by maintenance dosing if rapid titration is desired OR initiated with maintenance dosing without a loading dose Solution, tablet: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose (10 to 15 µg/kg) followed by maintenance dosing (3.4 to 5.1 µg/kg/day) if rapid titration is desired OR initiated with maintenance dosing (3.4 to 5.1 µg/kg/day) without a loading dose	be either initiated with a loading dose (10 to 15 µg/kg) followed by maintenance dosing (3.4 to 5.1 µg/kg/day) if rapid titration is desired OR initiated with maintenance dosing (3.4 to 5.1 µg/kg/day) without a loading dose <u>Increase myocardial contractility in pediatric patients with heart failure in children 5 to 10 years of age:</u> Injection: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose followed by maintenance dosing if rapid titration is desired OR initiated with maintenance dosing without a loading dose Solution, tablet: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose (20 to 45 µg/kg) followed by maintenance dosing (6.4 to 12.9 µg/kg/day OR 3.2 to 6.4 µg/kg/day twice daily) if rapid titration is desired OR initiated with maintenance dosing (3.4 to 5.1 µg/kg/day) without a loading dose	

*Parenteral administration of digoxin should be used only when the need for rapid digitalization is urgent or when the drug cannot be taken orally. Intramuscular injection can lead to severe pain at the injection site; therefore, intravenous administration is preferred. If the drug must be administered by the intramuscular route, it should be injected deep into the muscle followed by massage.

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with the Cardiotonic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atrial Fibrillation				
Hallberg et al.[11] (2007) AF group: Patients with atrial fibrillation on digoxin vs patients with atrial fibrillation not on digoxin CHF group: patients with CHF on digoxin vs patients with CHF not on digoxin AF and CHF group: Patients with atrial fibrillation and CHF on digoxin vs patients with AF and CHF not on	Cohort AF group: ECG finding of atrial fibrillation at admission, at discharge or had a discharge diagnosis of atrial fibrillation CHF group: History of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission AF and CHF group: ECG finding of atrial fibrillation on admission, ECG finding of atrial fibrillation at discharge or a discharge diagnosis of atrial fibrillation, and a medical history of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission	N=60,764 1 year	Primary: One year mortality Secondary: Effects on LVEF, s-creatinine and AMI	Primary: Patients with AF who received digoxin did significantly worse than those AF patients who did not receive digoxin therapy (RR of death was 1.42; 95% CI, 1.29 to 1.56). Patients with CHF who received digoxin therapy did significantly worse than those CHF patients who did not receive digoxin therapy (RR of death was 1.11; 95% CI, 1.04 to 1.19). In the group of patients with AF and CHF, there was no mortality difference between those that received digoxin therapy and those that did not receive digoxin therapy (RR of death was 1.00; 95% CI, 0.94 to 1.06). Secondary: In patients with an LVEF of ≤30%, there was not a significant difference in rate of death between patients who received digoxin therapy and those that did not (RR of death was 1.06; 95% CI, 0.86 to 1.31). In patients with an LVEF of >30%, there was not a significant difference in rate of death between patients who received digoxin therapy and those that did not (RR of death was 1.14; 95% CI, 0.98 to 1.32). Regardless of level of s-creatinine (low, normal, high), there was not a significant difference in mortality between those who received digoxin therapy and those who did not: low s-creatinine (RR of death was 1.23; 95% CI, 0.91 to 1.66), normal s-creatinine (RR of death was 1.22; 95% CI, 0.94 to 1.58), high s-creatinine (RR of death was 0.98; 95% CI, 0.83 to 1.16) respectively. In patients with an AMI, the RR for death was 1.17; 95% CI, 1.10 to 1.24 between those that received digoxin therapy and those that did not receive digoxin therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
digoxin				In patients without an AMI, the RR for death was 1.10; 95% CI, 1.04 to 1.16 between those that received digoxin therapy and those that did not receive digoxin therapy.
Turakhia et al.[12] (2014) TREAT-AF Patients on digoxin vs patients not on digoxin	Cohort, RETRO Patients with newly diagnosed, nonvalvular atrial fibrillation/flutter seen within 90 days of diagnosis in an outpatient VA care setting	N=122,465 353,168 person-years of follow-up	Primary: Cumulative mortality rates Secondary: Not reported	Primary: Digoxin treatment was significantly associated with death in the multivariate Cox regression model (HR, 1.26; 95% CI, 1.23 to 1.29; P<0.001) and after propensity matching (HR, 1.21; 95% CI, 1.17 to 1.25; P<0.001). Subgroup findings were similar to the point estimates for the full and propensity-matched cohorts. There was evidence of possible effect modification in the full cohort and increased risk in patients with prior MI (P=0.002 in the full cohort; P=0.077 in the propensity-matched cohort). In all other subgroups, tests for interaction were not significant in full and propensity-matched analyses. Secondary: Not reported
Shah et al.[13] (2014) <u>Patients with HF:</u> patients on digoxin vs patients not on digoxin <u>Patients without HF:</u> patients on digoxin vs patients not on digoxin	Cohort, RETRO Patients aged ≥65 years admitted to a hospital with a primary or secondary diagnosis of AF	N=27,972 (propensity matched cohort of patients with AF and HF) N=46,262 (propensity matched cohort of patients with AF and without HF) 3.0 to 4.2 years mean follow-up time	Primary: All-cause mortality Secondary: Not reported	Primary: In the propensity score–matched cohort of patients with concomitant AF and HF, digoxin use was associated with a 14% greater risk of all-cause mortality (adjusted HR, 1.14; 95% CI, 1.10 to 1.17) and a similar result was observed with unadjusted analysis in this cohort (unadjusted HR, 1.14; 95% CI, 1.11 to 1.17). In the propensity score–matched cohort of patients with AF and without HF, digoxin use was associated with a 17% greater risk of all-cause mortality (adjusted HR, 1.17; 95% CI, 1.14 to 1.19) and a similar result was observed with unadjusted analysis in this cohort (unadjusted HR, 1.16; 95% CI, 1.13 to 1.19). There was a significant interaction between digoxin and gender (P=0.008), in which risk of all-cause mortality was greater in men compared with women (21 vs 13%).
Khand et al.[14] (2003)	DB, PC, PG, RCT	N=47	Primary: Assessment of	Primary: *Phase 1:*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Phase 1: Digoxin with placebo vs digoxin with carvedilol Phase 2: digoxin vs carvedilol	Patients with persistent AF for >1 month and heart failure who were receiving digoxin and diuretics	Phase 1: 4 months Phase 2: 6 months	LVEF, ventricular rate control, symptom improvement, exercise test Secondary: Not reported	The patients in the digoxin with carvedilol group experienced a reduction in mean ventricular rate compared to the patients in the digoxin with placebo group (65.2±15 vs 74.9±11.2, respectively; P<0.0001). The patients in the digoxin with carvedilol group experienced improved LVEF compared to the patients in the digoxin with placebo group (30±9.6 vs 26±12.4, respectively; P=0.048). The patients in the digoxin with carvedilol group experienced an improvement in symptom scores compared to the patients in the digoxin with placebo group (7 [3 to 12.5] vs 8 [3 to 15], respectively; P=0.039). The patients in the digoxin with carvedilol group experienced a reduced ventricular rate at rest and throughout steady-state exercise (peak ventricular rate 106 beats/min) compared to those patients in the digoxin with placebo group (peak ventricular rate 123 beats/min; P<0.05). *Phase 2:* There was no significant difference in ventricular rate control between the digoxin and the carvedilol treatment groups (88.8±18.7 vs 75.7±10.6, respectively; P=0.13). There was no significant difference in LVEF between the digoxin and the carvedilol treatment groups (21.6±11 vs 27.2±11.7, respectively; P=0.15). There was no significant difference in symptom scores between the digoxin and the carvedilol treatment groups (6 [2 to 17] vs 8 [5 to 15.5], respectively; P=0.08). There was no significant difference in ventricular rate at steady-state exercise between the digoxin and the carvedilol treatment groups. Secondary: Not reported
Koh et al.[15] (1995) Digoxin 0.125 to 0.5 mg QD plus	PRO, RCT, XO Patients with persistent AF for >1 month	N=37 7 months	Primary: Effects on ventricular rate, BP, rate-pressure, maximal exercise	Primary: Patients in the digoxin plus betaxolol group experienced a significant reduction in ventricular rates both at rest and during exercise (67±3 and 135±5 beats/min, respectively) compared to the patients in the digoxin plus diltiazem group (80±7 and 154±5 beats/min, respectively; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diltiazem 90 mg BID vs digoxin 0.125 to 0.5 mg QD plus betaxolol QD			tolerance Secondary: Safety	Patients in the digoxin plus betaxolol group experienced a significant reduction in SBP during maximal exercise (164±4 mm Hg) but not at rest (127±3 mm Hg) compared to the patients in the digoxin plus diltiazem group (173±4 and 130±4 mm Hg, respectively; P<0.05, P>0.05, respectively). Patients in the digoxin plus betaxolol group experienced significantly less rate-pressure products at rest (85±4 x 10^2 mm Hg/min) and during exercise (213±12 x 10^2 mm Hg/min) compared to the patients in the in digoxin plus diltiazem group (105±6 and 269±12, respectively; P<0.05 for both). Both the digoxin plus betaxolol group and the digoxin plus diltiazem group experienced a significant improvement in exercise capacity compared to baseline (P<0.05), but the groups were not statistically significant from one another (9.3±0.5 vs 9.7±0.5 MET; P>0.05). There were no statistical differences between the treatment groups in any of the efficacy points measured between time points at weeks four and seven months. Secondary: No patients withdrew from the study in either treatment groups due to side effects. The digoxin plus betaxolol group experienced more side effects, which were considered minimal, compared to the digoxin plus diltiazem group. The minimal side effects observed in the digoxin plus betaxolol group included dyspnea, gastric pain, fatigue and constipation.
Hemels et al.[16] (2006) Group 1: Digoxin 0.125 to 0.25 mg QD plus acute (within 24 hours) ECV vs digoxin 0.125 to 0.25 mg QD plus	MC, PRO, RCT Patients with persistent AF, defined as non–self-terminating arrhythmia and requiring ECV to obtain sinus rhythm), and no contraindications to anticoagulation therapy	N=144 18 months	Primary: Freedom from permanent AF Secondary: QOL	Primary: At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent AF between the acute and routine ECV groups (32%; 95% CI, 22 to 44 vs 31%; 95% CI, 21 to 44, respectively; P=0.85), despite more ECVs in the acute vs the routine group ([median 3 vs 2 ECVs; P<0.05] and [≥3 ECVs in 54 vs 33% of patients, respectively; P<0.01]). At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent AF between the verapamil and digoxin groups (28%; 95% CI, 19 to 40 vs 36%; 95% CI, 25 to 48, respectively; P=0.33), despite more ECVs in the digoxin group compared to the verapamil group ([median 3 vs 2 ECVs, respectively; P<0.001] and [≥3

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
routine ECV Group 2: verapamil 120 to 360 mg QD with acute (within 24 hours) ECV vs verapamil 120 to 360 mg QD plus routine ECV Study medications were dosed to reach a target heart rate <100 beats/min and were administered for 4 weeks before ECV and continued during total follow-up. ECV was done one month after randomization and was only performed if anticoagulation therapy had been adequate (goal INR 2.5 to 3.5).				ECVs in 60 vs 28% of patients, respectively; P<0.001]). Secondary: At the end of the 18 month follow-up period, there were no significant differences in QOL between the acute and the routine cardioversion groups. Also, at the end of the 18 months, there were no significant differences in QOL between the digoxin and verapamil groups.
Wyse et al.[17] (2002) AFFIRM Rhythm control therapy:	MC, RCT Patients 65 years and older who had AF that was likely recurrent, AF was	N=4,060 3.5 years	Primary: Overall mortality Secondary: Composite death, disabling stroke,	Primary: The difference in mortality between the two groups was not significant (HR, 1.15; 95% CI, 0.99 to 1.34; P=0.08). Secondary: The rates of the composite end point of death, disabling stroke, disabling

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm) vs rate control therapy: β-blockers, calcium-channel blockers, digoxin, and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm)	likely to cause illness or death, long-term treatment for AF was warranted, no contraindicated to anticoagulation therapy, eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after randomization		disabling anoxic encephalopathy, major bleeding, or cardiac arrest	anoxic encephalopathy, major bleeding, or cardiac arrest were also similar in the two groups (P=0.33).
Gheorghiade et al.[18] (2013) AFFIRM Patients taking digoxin vs	Post hoc analysis of AFFIRM Patients enrolled in the AFFIRM trial taking digoxin as initial therapy	N=1,756 3.5 years	Primary: All-cause mortality Secondary: all-cause mortality at 1, 2, 3, and 12 months of follow-up	Primary: All-cause mortality occurred in 14 and 13% of matched patients receiving and not receiving digoxin as an initial therapy, respectively (P=0.540). Secondary: Digoxin had no association with mortality at one month (P=0.421), two months (P=0.997), three months (P=0.620), or 12 months (P=0.612) of follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propensity-matched patients not taking digoxin				
Whitbeck et al.[19] (2013) AFFIRM Patients taking digoxin vs propensity-matched patients not taking digoxin	Post hoc analysis of AFFIRM Patients enrolled in the AFFIRM trial (analyses were conducted in all patients and in subsets according to the presence or absence of HF)	N=4,060 3.5 years	Primary: All-cause mortality, CV mortality Secondary: Not reported	Primary: Digoxin was associated with an increase in all-cause mortality [estimated hazard ratio (EHR), 1.41; 95% CI 1.19 to 1.67; P<0.001], CV mortality (EHR, 1.35; 95% CI, 1.06 to 1.71; P=0.016), and arrhythmic mortality (EHR, 1.61; 95% CI, 1.12 to 2.30; P=0.009). The all-cause mortality was increased with digoxin in patients without or with HF (EHR, 1.37; 95% CI, 1.05 to 1.79; P=0.019 and EHR, 1.41; 95% CI, 1.09 to 1.84; P=0.010, respectively). The greatest change in the EHR followed addition of NYHA functional class, with a decrease from 1.66 (95% CI, 1.42 to 1.94; P<0.001) to 1.49 (95% CI, 1.27 to 1.74; P<0.001). There was no significant digoxin–gender interaction for all-cause (P=0.70) or cardiovascular (P=0.95) mortality. Secondary: Not reported
Okin et al.[20] (2015) Losartan-based treatment vs atenolol-based treatment	Post-hoc analysis of a substudy of the Losartan Intervention For Endpoint Reduction in hypertension (LIFE) trial Hypertensive patients with ECG left ventricular hypertrophy in AF at baseline or who developed AF during follow-up stratified by digoxin use	N=937 4.7±1.1 years of mean follow-up	Primary: All-cause mortality, and cardiovascular and sudden cardiac death Secondary: Not reported	Primary: Among 937 hypertensive patients who were in atrial fibrillation at baseline or developed atrial fibrillation during follow-up, 372 patients (39.7%) were treated with digoxin during follow-up and 565 patients (60.3%) were never on digoxin. During follow-up, 167 patients died (17.8%) from any cause, including 109 cardiovascular deaths (11.6%) and 40 sudden cardiac deaths (4.3%). In univariate Cox analyses, in-treatment digoxin use, entered as a time-varying covariate, was associated with a 61% higher risk of dying (HR, 1.61; 95% CI, 1.18 to 2.19; P=0.003). After adjusting for other univariate predictors of death in this population, including age, diabetes, history of ischemic heart disease, stroke, or heart failure, baseline Cornell product, QRS duration, heart rate, serum glucose, creatinine and high-density lipoprotein cholesterol, and a propensity score for digoxin use entered as standard covariates, and for in-treatment heart rate, pulse pressure, and Sokolow-Lyon voltage treated as time-varying covariates, digoxin use was no longer a significant predictor of mortality (HR, 1.04; 95% CI, 0.73 to 1.48; P=0.839).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In parallel analyses excluding the 175 patients on digoxin at baseline, in-treatment digoxin use was no longer a univariate (HR, 1.10; 95% CI, 0.71 to 1.68) or multivariate (HR, 0.84, 95% CI, 0.53 to 1.32) predictor of death. Similarly, if the 45 patients with a history of heart failure were excluded, in-treatment digoxin use was of borderline significance in univariate analyses (HR, 1.38; 95% CI, 0.99 to 1.93) but was not a significant predictor of death in multivariate Cox analyses (HR, 0.96; 95% CI, 0.65 to 1.39). Of note, in-treatment digoxin use had statistically similar performance in relevant subsets of the population, with no significant interactions between in-treatment digoxin use and sex (P=0.114), randomized treatment (P=0.536), history of heart failure (P=0.258) or ischemic heart disease (P=0.258), or in-treatment potassium levels (P=0.591) in Cox analyses. Secondary: Not reported
Van Gelder et al.[21] (2002) RACE Rhythm control therapy: electrical cardioversion, then sotalol 160 to 320 mg (based on weight and renal function); if recurrence within 6 months, repeat electrical cardioversion, then flecainide 200 to 300 mg QD or propafenone 450 to 900 mg QD; if recurrence again, electrical cardioversion repeated along	MC, RCT Patients with recurrent persistent AF or atrial flutter, who have undergone one electrical cardioversion during the previous 2 years, with a maximum of 2	N=522 2 years	Primary: Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse effects of antiarrhythmic drugs Secondary: Not reported	Primary: The composite end point occurred in 44 (17.2%) patients in rate-control group and in 60 (22.6%) patients in the rhythm-control group (absolute difference of -5.4; 90% CI, -11.0 to 0.4). Death from cardiovascular causes occurred in 18 (7.0%) patients in rate-control group and in 18 (6.8%) patients in the rhythm-control group (absolute difference of 0.2; 90% CI, -3.4 to 3.9). Heart failure occurred in nine (3.5%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of -1.0; 90% CI, -3.8 to 1.8). Thromboembolic complications occurred in 14 (5.5%) patients in rate-control group and in 21 (7.9%) patients in the rhythm-control group (absolute difference of -2.4; 90% CI, -6.0 to 1.2). Bleeding occurred in 12 (4.7%) patients in rate-control group and in nine (3.4%) patients in the rhythm-control group (absolute difference of 1.3; 90% CI, -1.5 to 4.1). Severe adverse effects of antiarrhythmic drugs occurred in two (0.8%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with amiodarone 600 mg QD for 4 weeks then 200 mg QD vs rate control therapy: digitalis, non-dihydropyridine calcium channel blocker, and β-blocker, alone or in combination				group (absolute difference of -3.7; 90% CI, -6.0 to -1.4). A pacemaker was implanted in three (1.2%) patients in rate-control group and in eight (3.0%) patients in the rhythm-control group (-1.8; 90% CI, -3.9 to 0.2). Secondary: Not reported
Van Gelder et al.[22] (2010) RACE II Lenient rate control (resting heart rate <110 bpm) vs strict rate control (resting heart rate <80 bpm and heart rate during moderate exercise <100 bpm) During the dose-adjustment phase, patients were administered one or more negative dromotropic drugs	MC, NI, OL, PRO, RCT Patients ≤80 years with permanent AF for up to 12 months, mean resting heart rate>80 bpm, and current use of oral anticoagulation therapy (or aspirin)	N=614 Up to 2 years of follow-up (3 years maximum)	Primary: Composite of death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, major bleeding, and arrhythmic events Secondary: Components of the primary, all-cause mortality, symptoms, functional status	Primary: Eighty-one patients (38 patients receiving lenient rate control vs 43 patients receiving strict rate control) reached the primary outcome. The three year estimated cumulative incidence was 12.9 vs 14.9% receiving lenient rate control and strict rate control, with an absolute difference between lenient control and strict control of -2.0 percentage points (90% CI, -7.6 to 3.5) and a HR of 0.84 (90% CI, 0.58 to 1.21). As compared to strict rate control, lenient rate control was noninferior with regard to the prevention of the primary outcome, for both the criteria of the difference in risk (P<0.001) and the HR (P=0.001). The HR was 0.80 (90% CI, 0.55 to 1.17) after statistical adjustment for the unbalanced distribution of the presence of coronary artery disease, the use of statins, and the diastolic blood pressure. Secondary: A total of 2.9 and 3.9% of patients receiving lenient rate control and strict rate control died from cardiovascular causes (HR, 0.79; 90% CI, 0.38 to 1.65). A total of 3.8 vs 4.1% of patients were admitted for heart failure (HR, 0.97; 90% CI, 0.48 to 1.96). A total of 1.6 vs 3.9% of patients experienced a stroke (HR, 0.35; 90% CI, 0.13 to 0.92). A total of 5.3 vs 4.5% of patients experienced major bleeding (HR, 1.12; 90% CI, 0.60 to 2.08). All-cause mortality occurred in 17 patients receiving lenient rate control (5.6% at three years) compared to 18 patients receiving strict rate control (6.6% at three years; HR, 0.91; 90% CI, 0.52 to 1.59). Death from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(i.e., beta-blockers, non-dihydropyridine calcium channel blockers, and digoxin), used alone or in combination and at various doses, until the heart-rate target or targets were achieved.				noncardiovascular causes occurred in eight and seven patients receiving lenient and strict rate control. At the end of the follow-up period, 129/283 (45.6%) and 126/274 (46.0%) of patients receiving lenient and strict rate control had symptoms associated with AF (P=0.92); dyspnea (30.0 vs 29.6%; P=0.90), fatigue (24.4 vs 22.6%; P=0.63), and palpitations (10.6 vs 9.5%; P=0.66). At the end of follow-up period, in the lenient rate control group and in the strict control group, 70.0 and 70.4% of patients, respectively, were in NYHA functional class I, 23.3 vs 23.4% were in class II, and 6.7 vs 6.2% were in class II (P=0.74 for all comparisons).
Groenveld et al.[23] (2011) RACE II Lenient rate control (resting heart rate <110 bpm) vs strict rate control (resting heart rate <80 bpm and heart rate during moderate exercise <100 bpm) During the dose-adjustment phase, patients were administered one or more negative dromotropic drugs (i.e., beta-blockers, non-dihydropyridine	Post-hoc analysis of RACE II Patients ≤80 years with permanent AF for up to 12 months, mean resting heart rate>80 bpm, and current use of oral anticoagulation therapy (or aspirin)	N=614 Up to 2 years of follow-up (3 years maximum)	Primary: QOL (SF-36), AF severity scores (MFI-20) Secondary: Not reported	Primary: At the end of follow-up all SF-36 subscales were comparable between patients receiving lenient and strict rate control. At baseline and at the end of the trial there were no differences in the MFI-20 subscales between patients receiving lenient and strict rate control. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
calcium channel blockers, and digoxin), used alone or in combination and at various doses, until the heart-rate target or targets were achieved.				
Opolski et al.[24] (2004) HOT CAFÉ Rhythm control therapy: propafenone 450 to 600 mg QD, disopyramide 300 to 600 mg QD, or sotalol 160 to 320 mg QD vs rate control therapy: β-blockers, non-dihydropyridine calcium channel blockers, digoxin, or a combination of these drugs. All patients underwent electric cardioversion prior to the initiation of study medication.	MC, OL, RCT Patients between 50 to 75 years of age with AF known to be present continuously for between seven days and two years with acceptable etiology of the arrhythmia related to ischemic heart disease, arterial hypertension, hemodynamically insignificant valvular heart disease, or lack of assessable etiology	N=205 1 year	Primary: Composite of death from any cause (thromboembolic complications and intracranial or other major hemorrhage) Secondary: Rate control, sinus rhythm maintenance, discontinuation of therapy (proarrhythmic effects), hemorrhage, hospitalization, new or worsening CHF, or changes in exercise tolerance	Primary: There was not a significant difference in composite of death from any cause between the rate control group and the rhythm control group (OR, 1.98; 95% CI, 0.28 to 22.3; P>0.71). Secondary: The patients in the rhythm control group had a significantly lower mean heart rate (79.1±8.6 beats/min) in 24-hour Holter monitoring compared to the patients in the rate control group (85.8±7.5 beats/min; P<0.003). Four patients in the rhythm control group experienced proarrhythmic effects. Whether this lead to discontinuation of therapy was not mentioned. At the end of the study, 66 patients (63.5%) in the rhythm control arm were in sinus rhythm, with 27 of these patients successfully maintained with the first antiarrhythmic compound administered after the first cardioversion. There was not a statistical difference seen in bleeding complications between the rhythm control group (eight patients) and rate control group (five patients). A significantly lower number of hospitalizations were seen in the rate control arm compared to the rhythm control arm (12 vs 74%, respectively; P<0.001). Both the rhythm control group and rate control group had significant improvements in CHF class at some point during follow-up compared to baseline (P<0.001 and P<0.05, respectively). No difference in NYHA functional class between patients initially randomized to the two strategies was found at the end of the follow-up period.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At the end of the study, both maximal workload and exercise duration were higher in the rhythm control arm compared to the rate control arm (P<0.001 and P<0.001, respectively).
Lafuente-Lafuente et al.[25] (2009) Antiarrhythmic drugs (amiodarone, aprindine, azimilide, bidisomide, flecainide, disopyramide, dofetilide, dronedarone, quinidine, propafenone, sotalol) vs placebo, drugs for rate control (digoxin, calcium channel blockers, β-blockers) or no treatment	MA (45 trials) Adults >16 years of age who had AF of any type and duration and in whom sinus rhythm had been restored, spontaneously or by any therapeutic intervention	N=12,559 Variable duration	Primary: Mortality, embolic complications, adverse events Secondary: Use of anticoagulation, recurrence of AF	Primary: No deaths were reported with flecainide in the three trials. Quinidine showed a trend to increase mortality compared to controls (OR, 2.26; 95% CI, 0.93 to 5.45; P=0.07). This trend was significant if missing patients were counted as deaths (OR, 2.29; 95% CI, 1.05 to 5.01; P=0.04), and when class IA drugs (quinidine and disopyramide) were combined (OR, 2.39; 95% CI 1.03 to 5.59; P=0.04). The number NNH for class IA drugs was 109 patients treated for one year to have one excess death. Sotalol showed a trend to increased mortality (OR, 2.09; 95% CI, 0.97 to 4.49; P=0.06) compared to controls. This trend was significant if missing patients were counted as deaths (OR, 2.27; 95% CI, 1.36 to 3.77; P=0.002). Amiodarone was associated with a reduction in mortality compared to combined class I drugs (OR, 0.39; 95% CI, 0.19 to 0.79; NNT 17). When compared to controls, amiodarone showed no significant difference in mortality. No other significant difference in mortality was detected, either vs control or between different antiarrhythmics. The analysis of cardiovascular mortality gave the same results as that of all-cause mortality. Only five of the 30 studies comparing antiarrhythmics with a control reported stroke outcomes. They reported six strokes in 650 patients in the control groups and 20 strokes in 1,755 patients treated with antiarrhythmics. Withdrawals due to adverse effects were more frequent with all drugs, except aprindine and dofetilide, compared to controls. Pooled events rates varied from 9 to 23% for withdrawals due to adverse effects. The mean number of patients needed to treat for one year to have one excess withdrawal from treatment ranged from nine (quinidine) to 27 (amiodarone, propafenone, or sotalol). Quinidine caused more withdrawals than the other class I drugs (OR, 2.25; 95% CI 1.45 to 3.51; P=0.0003). Amiodarone produced significantly fewer withdrawals than other class I drugs combined

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(OR, 0.52; 95% CI, 0.34 to 0.81; P=0.004). All antiarrhythmics increased proarrhythmic effects, with the exception of amiodarone and propafenone. Pooled events rates varied from 1 to 7% for proarrhythmia. The NNH for proarrhythmia ranged between 17 (flecainide) and 119 (dofetilide). Amiodarone produced significantly less proarrhythmic events than other class I drugs combined (OR, 0.28; 95% CI, 0.13 to 0.59; P=0.0007). Secondary: All class IA, class IC and class III drugs significantly reduced the recurrence of atrial fibrillation. Pooled recurrence rates of atrial fibrillation at 1 year were 71 to 84% in controls and were reduced to 42% to 67% in patients treated with antiarrhythmics. The NNT for one year to avoid one recurrence of atrial fibrillation were three with amiodarone, four with flecainide, five with dofetilide and propafenone, eight with quinidine and sotalol and 10 with dronedarone. Amiodarone reduced recurrences of AF significantly more than combined class I drugs (OR, 0.31; 95% CI, 0.21 to 0.45; P<0.0001) and more than sotalol (OR, 0.43; 95% CI 0.29 to 0.64; P<0.0001). No other differences between antiarrhythmics were detected. Chronic anticoagulation with warfarin was mandatory in only three studies. The decision on anticoagulation was left to the judgment of the attending physician in the remaining studies.
Heart Failure				
Koh, Kwan et al.[26] (1995) Without digoxin, diltiazem, or betaxolol (Group I) vs digoxin 0.125 to 0.5 mg QD (Group II)	PRO, RCT Patients with chronic heart failure for >1 month	N=45 4 weeks	Primary: Heart rate, BP, rate-pressure Secondary: Not reported	Primary: Resting ventricular rates were lower in all patients receiving active treatment (groups II, III, IV) compared those patients in group I who did not receive digoxin (P<0.01). Ventricular rates during exercise were lower in groups III and IV compared to groups I and II (P<0.01). No significant differences in ventricular rate were noted between groups III and IV, either at rest or during exercise (P<0.01). SBP was not significantly different between the four groups (P=0.09). Rate-pressure product at rest and during exercise was significantly lower in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs digoxin 0.125 to 0.5 mg QD and diltiazem 90 mg BID (Group III) vs digoxin 0.125 to 0.5 mg QD and betaxolol 20 mg QD (Group IV)				groups III and IV compared to groups I and II (P<0.01). Secondary: Not reported
DIG[27] (1997) Digoxin 0.125 to 0.5 mg QD vs placebo Patients continued on their other CHF therapies (including diuretics and ACE inhibitor). Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	DB, MC, PC, RCT Patients ≥21 years old with heart failure and LVEF ≤45% who were in normal sinus rhythm	N=6,800 37 months	Primary: Mortality Secondary: Mortality from cardiovascular causes, death from worsening heart failure, hospitalization for worsening heart failure, and hospitalization for other causes (specifically due to digoxin toxicity)	Primary: In the digoxin group, there were 1,181 (34.8%) deaths compared to 1,194 (35.1%) deaths in patients receiving placebo (95% CI, 0.91 to 1.07; P=0.80). Secondary: In the digoxin group, 1,016 (29.9%) patients died from cardiovascular compared to 1,004 (29.5%) patient deaths in the placebo group (95% CI, 0.93 to 1.10; P=0.78). There were 394 deaths in the digoxin group that were attributed to worsening heart failure compared to 449 deaths in the placebo (95% CI, 0.77 to 1.01; P=0.06). In the digoxin group, 910 patients were hospitalized for worsening heart failure compared to 1,180 patients in the placebo group (95% CI, 0.66 to 0.79; P<0.001). Overall, the placebo group had a significantly higher number of patients hospitalized compared to the digoxin group, 2,184 vs 2,282 respectively (95% CI, 0.87 to 0.98; P<0.006). Other reasons for hospitalizations included cardiac events and respiratory infection. There was a statistically significantly higher number of patients in the digoxin group hospitalized for suspected digoxin toxicity compared to placebo, 67 vs 31, respectively (95% CI, 1.42 to 3.32; P<0.001).
Ather et al.[28]	Post-hoc analysis of	N=6,800	Primary:	Primary:

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(2011) DIG Digoxin 0.125 to 0.5 mg QD vs placebo	DIG Patients ≥21 years old with heart failure and LVEF ≤45% who were in normal sinus rhythm; the DIG database was partitioned into 20 clusters	37 months	Multivariate Cox regression analyses were used to identify clusters in which digoxin is associated with either an increase ($Mortality_{dig}HR>1$), decrease ($Mortality_{dig}HR<1$), or no association with all-cause mortality ($Mortality_{dig}HR$-NS); and separately, with an increase ($HFA_{dig}HR>1$), decrease ($HFA_{dig}HR<1$), or no association with heart failure admissions ($HFA_{dig}HR$-NS) Secondary: Not reported	Nine hundred and thirty-eight patients were identified in the $Mortality_{dig}HR>1$ group, 6,818 patients in the $Mortality_{dig}HR$-NS group, and non in the $Mortality_{dig}HR<1$. The $Mortality_{dig}HR>1$ group had a higher prevalence of females, diabetes, hypertension, higher age, SBP, heart rate, and ejection fraction compared to the $Mortality_{dig}HR$-NS group. Six thousand three hundred and twenty-five patients were identified in the $HFA_{dig}HR<1$ group, 1,431 patients in the $HFA_{dig}HR$-NS group, and none in the $HFA_{dig}HR>1$ group. The $HFA_{dig}HR$-NS group had a higher prevalence of females and hypertension, higher SBP, body mass index, and ejection fraction; and lower prevalence of peripheral edema and third heart sound compared to the $HFA_{dig}HR<1$ group. Secondary: Not reported
Meyer et al.[29] (2008) DIG Digoxin 0.125 to 0.5mg QD vs placebo The majority of	Subgroup analysis of DIG trial (comparing equal numbers of patients with systolic [n=916] and diastolic heart failure [916]) Patients ≥21 years old with chronic heart failure and	N=1,832 2 to 3.2 years	Primary: Heart failure hospitalization or heart failure mortality (combined and separately) at the end of 3.2 years and 2 years of follow-up Secondary:	Primary: After 3.2 years of median follow-up, the combined end point of heart failure hospitalization or heart failure mortality occurred in 28 and 32% of patients with systolic heart failure (HR, 0.85; 95% CI, 0.67 to 1.08, P=0.188) and in 20 and 25% of patients with diastolic heart failure (HR, 0.79; 95% CI, 0.60 to 1.03; P=0.085) who were receiving digoxin and placebo, respectively. After 3.2 years of median follow-up, the effect of digoxin on heart failure hospitalization was similar in patients with systolic heart failure (HR, 0.80; 95% CI, 0.62 to 1.03, P=0.079) and diastolic heart failure (HR, 0.77; 95% CI, 0.57 to 1.03, P=0.074).

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patients enrolled were also receiving diuretics and ACE inhibitors	LVEF ≤45% who were in normal sinus rhythm		Not reported	At the end of two years of follow-up, the effect of digoxin on the combined end point was similar in patients with systolic heart failure (HR, 0.72; 95% CI, 0.55 to 0.95; P=0.022) and those with diastolic heart failure (HR, 0.69; 95% CI, 0.50 to 0.95; P=0.025). At the end of two years of follow-up, digoxin decreased heart failure hospitalization for systolic heart failure (HR, 0.73; 95% CI, 0.54 to 0.97; P=0.033) and diastolic heart failure (HR, 0.64; 95% CI, 0.45 to 0.90; P=0.010). Secondary: Not reported
Ahmed, Rich, Love et al.[30] (2006) DIG Digoxin 0.125 to 0.5 mg QD vs placebo QD Patients continued on their other CHF therapies (including diuretics and ACE inhibitors) Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	Post hoc analysis of DIG Patients with heart failure, regardless of ejection fraction, and who were in normal SR	N=5,548 40 months	Primary: All-cause mortality Secondary: Mortality due to cardiovascular causes and heart failure, hospitalizations due to all causes, cardiovascular causes, and worsening heart failure	Primary: At 40 months, all cause death rate was 33% in the placebo group, 29% in the group of patients with a SDC of 0.5 to 0.9 ng/mL, and 42% in the group of patients with the SDC of ≥1.0 ng/mL (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.77; 95% CI, 0.67 to 0.89; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 1.06; 95% CI, 0.93 to 1.20; P=0.406). Secondary: At 40 months, cardiovascular mortality rate was 26% in the placebo group, 24% in the SDC of 0.5 to 0.9 ng/mL group, and 33% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.83; 95% CI, 0.71 to 0.97; P=0.019 and placebo vs SDC ≥1 ng/mL; adjusted HR, 1.07; 95% CI, 0.93 to 1.24; P=0.339). At 40 months, mortality rate due to heart failure was 12% in the placebo group, 9% in the SDC of 0.5 to 0.9 ng/mL group, and 14% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.63; 95% CI, 0.49 to 0.82; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.87; 95% CI, 0.70 to 1.09; P=0.236). At 40 months, all cause hospitalization rates were 67% in the placebo group, 64% in the SDC of 0.5 to 0.9 ng/mL group, and 71% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.85; 95% CI, 0.78 to 0.92; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.95; 95% CI, 0.87 to 1.05; P=0.331). At 40 months, cardiovascular hospitalization rates were 53% in the placebo

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				group, 48% in the SDC of 0.5 to 0.9 ng/mL group, and 55% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.79; 95% CI, 0.72 to 0.88; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.91; 95% CI, 0.82 to 1.01; P=0.086). At 40 months, hospitalization rates due to heart failure were 33% in the placebo group, 23% in the SDC of 0.5 to 0.9 ng/mL group, and 29% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.62; 95% CI, 0.54 to 0.72; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.68; 95% CI, 0.59 to 0.79; P=0.086).
Gheorghiade et al.[31] (2013) Digoxin 0.125 to 0.5 mg QD vs placebo QD Patients continued on their other CHF therapies (including diuretics and ACE inhibitors) Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	Subanalysis of DIG Patients enrolled in the DIG trial in a high-risk subgroup (NYHA class III–IV symptoms, LVEF <25%, or cardiothoracic ratio (CTR) >55%)	NYHA class III–IV symptoms (N=2223), LVEF <25% (N=2256), and CTR>55% (N=2345). 2 years	Primary: Combined endpoints of HF mortality or HF hospitalization and all-cause mortality or all-cause hospitalization during the first 2 years after randomization Secondary: Not reported	Primary: Compared with patients receiving placebo, digoxin-associated HRs for the combined endpoint of 2-year HF death or HF hospitalization in subgroups with NYHA class III–IV symptoms, LVEF <25%, and CTR >55% were 0.65 [95% CI, 0.57 to 0.75; P<0.001], 0.61 (95% CI, 0.53 to 0.71; P<0.001), and 0.65 (95% CI, 0.57 to 0.75; P<0.001), respectively. Compared with the patients receiving placebo, digoxin-associated HRs for the combined endpoint of 2-year total death or all-cause hospitalization in subgroups with NYHA class III–IV symptoms, LVEF <25%, and CTR >55% were 0.88 (95% CI, 0.80 to 0.97; P=0.012), 0.84 (95% CI, 0.76 to 0.93; P=0.001), and 0.85 (95% CI, 0.77 to 0.94; P=0.002), respectively. Secondary: Not reported
Bourge et al.[32] (2013) Digoxin 0.125 to 0.5 mg QD	Subanalysis of DIG Patients enrolled in the DIG trial ≥65 years	N=3,405 30 days	Primary: 30-day all-cause hospital admission Secondary: 30-day	Primary: All-cause hospital admission occurred in 8.1 and 5.4% of older patients with HF and reduced ejection fraction assigned to placebo and digoxin, respectively (HR when digoxin was compared with placebo, 0.66; 95% CI, 0.51 to 0.86; P=0.002). This effect of digoxin remained unchanged when adjusted for baseline characteristics (HR, 0.65; 95% CI, 0.50 to 0.85;

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vs placebo QD Patients continued on their other CHF therapies (including diuretics and ACE inhibitors) Initial dosing of digoxin was based on patient's age, sex, weight and renal function.			cardiovascular and heart failure hospitalizations, 30-day all-cause mortality and cause-specific mortalities, and the composite outcome of 30-day all-cause hospitalization or mortality	P=0.002). Secondary: Patients in the digoxin group had a lower risk of 30-day cardiovascular (HR, 0.53; 95% CI, 0.38 to 0.72; P<0.001) and 30-day heart failure (HR, 0.40; 95% CI, 0.26 to 0.62; P<0.001) hospitalizations, with similar trends for 30-day total mortality that did not reach statistical significance because of a low number of events.
Abdul-Rahim et al.[33] (2016) DIG Digoxin 0.125 to 0.5 mg QD vs placebo QD Patients continued on their other CHF therapies (including diuretics and ACE inhibitors) Initial dosing of digoxin was based on patient's age, sex, weight and	Subanalysis of DIG Patients enrolled in the DIG trial stratified by diabetes status	N=6,800 4 years	Primary: Composite of CV death or heart failure hospitalization; composite of heart failure death or heart failure hospitalization; all-cause death Secondary: Not reported	Primary: Of the 6,800 patients randomized in DIG, 1,933 patients (28.4%) were reported by investigators to have diabetes. Overall, 1,653 placebo treated patients (rate 20.6 per 100 patient years) and 1,501 (rate 17.3) digoxin treated patients experienced the composite outcome of CV death or heart failure hospitalization (HR, 0.85; 95% CI, 0.79 to 0.91; P<0.001). Although the relative risk reduction with digoxin in patients with diabetes (10%) was numerically smaller than in those without diabetes (17%), the test for interaction was not significant (P=0.27). Overall, 1,004 placebo treated patients (rate 10.1 per 100 patient years) and 1,016 (rate 10.3) digoxin treated patients died from a CV death (HR, 1.01; 95% CI, 0.93 to 1.11; P=0.782). The lack of effect of digoxin on this outcome was similar, irrespective of diabetes status. Overall, 1,180 placebo treated patients (rate 14.7 per 100 patient years) and 910 (rate 10.5) digoxin treated patients were hospitalized at least once for heart failure (HR, 0.72; 95% CI, 0.66 to 0.79; P<0.001). The relative risk reduction with digoxin in patients with diabetes (21%) was numerically smaller than in patients without diabetes (31%) although the test for interaction was not significant (P=0.14).

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renal function.				Overall, 1,291 placebo treated patients (rate 16.1 per 100 patient years) and 1,041 (rate 12.0) digoxin treated patients experienced the composite outcome of heart failure death or heart failure hospitalization (HR, 0.75; 95% CI, 0.69 to 0.82; P<0.001). Although the relative risk reduction with digoxin in patients with diabetes (20%) was numerically smaller than in those without diabetes (27%), the test for interaction was not significant (P=0.30). Overall, 1,194 placebo treated patients (rate 12.1 per 100 patient years) and 1181 (rate 11.9) digoxin treated patients died from all-cause death (HR, 0.99; 95% CI, 0.91 to 1.07; P=0.801). The lack of effect of digoxin on this outcome was similar, irrespective of diabetes status. Secondary: Not reported
Ahmed et al.[34] (2006) Digoxin 0.125 to 0.5 mg QD vs placebo Patients continued on their other CHF therapies (including diuretics and ACE inhibitor). Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	MC, PC, RCT Patients with diastolic heart failure (LVEF >45%) and normal SR at baseline This was an ancillary trial conducted in parallel with the main DIG trial.[22]	N=988 37 months	Primary: Combined end point of heart failure hospitalization or heart failure mortality Secondary: Not prespecified, however the following outcomes were studied: all-cause and cardiovascular mortality, all-cause and cardiovascular hospitalizations, and the combined outcome of heart failure hospitalization and cardiovascular mortality	Primary: At the end of the study, there was not a statistically significant difference in the number of patients who experienced heart failure hospitalization or heart failure mortality between the digoxin group and the placebo group (102 [21%] vs 119 [24%], respectively; HR, 0.82; 95% CI, 0.63 to 1.07; P=0.136). Secondary: At the end of the study, there was not a statistically significant difference in the number of all-cause deaths between the digoxin group and the placebo group (115 [23%] vs 116 [23%], respectively; HR, 0.99; 95% CI, 0.76 to 1.28; P=0.925). Also, the difference in the number of cardiovascular deaths was not significantly different between the digoxin and the placebo group (81 patients in each group; HR, 1.00; 95% CI, 0.73 to 1.36; P=0.978). At the end of the study, there was not a statistically significant difference in the number of all-cause hospitalizations between the digoxin group and the placebo group (68% vs 67%, respectively; HR, 1.03; 95% CI, 0.89 to 1.20; P=0.683). Also, the difference in the number of cardiovascular hospitalizations was not significantly different between the digoxin and the placebo group (241 [49%] vs 225 [45%], respectively; HR, 1.10; 95% CI, 0.92 to 1.32; P=0.301). At the end of the study, there was not a statistically significant difference in the number of patients who experienced heart failure hospitalization or

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				cardiovascular mortality between the digoxin group and the placebo group (142 [29%] vs 154 [31%], respectively; HR, 0.88; 95% CI, 0.70 to 1.11; P=0.269).
Hashim et al.[35] (2014) Digoxin 0.125 to 0.5 mg QD vs placebo Patients continued on their other CHF therapies (including diuretics and ACE inhibitor). Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	MC, PC, RCT Patients with diastolic heart failure (LVEF >45%) and normal SR at baseline This was a substudy of patients ≥65 years in the ancillary trial conducted in parallel with the main DIG trial.	N=631 37 months	Primary: Hospitalization due to all causes occurring during the first 30 days after randomization Secondary: Cause-specific hospitalizations and mortality, and the combined end point of all-cause hospitalization or all-cause mortality during the first 30 days after randomization	Primary: Among patients aged ≥65 years, the main endpoint occurred in 3.8, 8.9, and 9.0% of patients in the placebo group, and those in the digoxin group receiving 0.125 mg, and ≥0.25 mg of digoxin a day, respectively (P=0.026). When compared with placebo, HR for 30-day all-cause admission for patients in the digoxin group as a whole was 2.46 (95% CI, 1.25 to 4.83). Secondary: There were six hospitalizations due to worsening heart failure, two of which occurred in the digoxin group (HR, 0.51; 95% CI, 0.09 to 2.79) and there were seven hospitalizations due to unstable angina, all but one occurred in the digoxin group (HR, 6.21; 95% CI, 0.75 to 51.62). Among the 357 patients <65 years, 30-day all-cause hospitalization occurred in 7.4 and 6.1% of patients in the placebo and digoxin groups, respectively (HR for digoxin, 0.80; 95% CI, 0.36 to 1.79). Digoxin had no significant effect on any other outcomes.
Uretsky et al.[36] (1993) PROVED Digoxin 0.125, 0.25, 0.375, or 0.5 mg QD vs placebo QD Digoxin was dosed to obtain a serum	DB, MC, PC, PG, RCT Patients ≥18 years old with NYHA Class II or III heart failure, normal sinus rhythm, receiving digoxin and diuretics, LVEF ≤35%, a LVED dimension of ≥60 mm or 34 mm/m^2	N=88 12 weeks	Primary: Treadmill time on maximal exercise testing, distance covered in a 6-minute walking test, incidence of treatment failure, time to treatment failure Secondary: Change in signs and symptoms of	Primary: At 12 weeks, patients in the placebo group experienced a median decline of 96 seconds in maximal exercise testing compared to a 4.5 second increase in the digoxin group (P=0.003). Digoxin did not display a significantly different effect on distance covered in a 6-minute walking test. Patients in the placebo group experienced a 39% rate of treatment failures compared to 19% in the digoxin group (P=0.039). The patients in the placebo group also experienced a decreased time to treatment failure compared to the digoxin group (P=0.037). Treatment failures included hospital admissions, increase in drug therapy and death.

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digoxin concentration of 0.9 to 2.0 ng/mL Patients continued on background therapy of diuretics.			heart failure, MLHF questionnaire, heart failure score, 7-point GEP, LVEF, vital signs, body weight	Secondary: At the end of the 12-week study, there was not a statistically significant difference between the placebo and digoxin groups in changes in signs and symptoms of heart failure, MLHF questionnaire or heart failure score. At the end of 12 weeks, patients in the digoxin group experienced a mean increase in LVEF by 2±2% compared to a mean decrease in LVEF of 3±2% for the patients in the placebo group (P=0.016). Heart rate and body weight were significantly lower in the digoxin group compared to the patients in the placebo group (P=0.03 and P=0.044, respectively).
Packer et al.[37] (1993) Digoxin QD vs placebo QD All patients started in an 8 week, single-blind run-in period during which the doses of background therapy for heart failure were adjusted to achieve optimal clinical benefits. After the run-in period, patients were randomized to either continue receiving digoxin therapy or receive placebo. Digoxin	DB, MC, PC, RCT Patients ≥18 years old with NYHA Class II or III heart failure, LVEF ≤35%, a LVED dimension of ≥60 mm or 34 mm/m^2, evidence of reduced exercise capacity, and normal sinus rhythm, who were clinically stable while receiving digoxin, diuretics, and an ACE inhibitor	N=178 12 weeks	Primary: Rates of withdrawal from the study due to worsening heart failure, time to withdrawal, changes in exercise tolerance Secondary: Effects of discontinuing digoxin therapy on symptoms, QOL, functional class, overall progress during the study and cardiac dimensions and function	Primary: Four patients who received digoxin, compared to 23 patients in the placebo group, withdrew from the study due to worsening of heart failure (P<0.001). The patients in the placebo group had a higher risk of worsening heart failure compared to the patients in the digoxin group over the 12 week study (RR, 5.9; 95% CI, 2.1 to 17.2; P<0.001). Exercise tolerance remained stable in patients receiving digoxin compared to deterioration in exercise tolerance in patients receiving placebo. The median difference in exercise duration between the two groups after 12 weeks was 42 seconds (P=0.006). Exercise endurance remained constant in patients receiving digoxin compared to a decrease in patients receiving placebo. The median difference in submaximal exercise endurance between the two groups after 10 weeks was 41 meters (P=0.01). Secondary: Of the patients in the placebo group, 38% experienced worsening dyspnea and fatigue compared to 16 and 18% of patients in the digoxin group (P=0.14 and P=0.04, respectively). Thirty-three percent of patients in the placebo group experienced a less of an improved quality of life compared to 47% in the digoxin group (P=0.04). Also, 48% of patients in the placebo group experienced a more frequent decline in quality of life compared to 41% in the digoxin group (P=0.04).

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was dosed to obtain a serum digoxin concentration of 0.9 to 2.0 ng/mL Patients continued on background therapy of diuretics and an ACE inhibitor.				In the placebo group, 27% of patients were reported as having a deterioration in NYHA class compared to 10% of patients in the digoxin group (P=0.019). Thirty-one percent of patients in the placebo group reported that they felt moderately worse or much worse, compared to 9% of patients in the digoxin group (P=0.007).
Dhaliwal et al.[38] (2008) Digoxin, renin-angiotensin inhibition and beta-blockade vs renin-angiotensin inhibition and beta-blockade	RETRO Patients with a diagnosis of congestive heart failure with depressed LVEF (≤45%) and who were on a regimen of rennin-angiotensin inhibitor(s) and beta-blocker(s) with or without digoxin	N=347 26 months	Primary: Combined and individual rates of heart failure-related hospitalizations and total mortality Secondary: Not reported	Primary: In the adjusted analysis, heart failure hospitalizations (HR, 1.08; 95% CI, 0.77 to 1.50; P=0.66), total mortality (HR, 1.03; 95% CI, 0.78 to 1.35, P=0.85), and the combined end point of heart failure hospitalization and total mortality (HR, 1.11; 95% CI 0.81 to 1.53, P=0.52) were similar between individuals who had digoxin as part of their drug regimen and those who did not. In unadjusted analyses, digoxin use was associated with a nonsignificant increase in heart failure hospitalization rates. The combined endpoint of heart failure hospitalization and total mortality and individual end points were not different between patients on digoxin therapy and those not on digoxin therapy in any of the prespecified analyses according to subgroups of ejection fraction (≤25 vs >25%), NYHA class (III or IV vs I or II), use vs nonuse of β-blockers, presence or absence of atrial fibrillation, and admission or discharge heart rates of ≤60 or ≥60 beats/minute. Secondary: Not reported
Fauchier et al.[39] (2009) Digoxin vs beta-blockers	RETRO Patients with primary or secondary diagnosis of both AF and heart failure between January 2000 and January	N=1,269 881 days	Primary: All cause mortality Secondary: Not reported	Primary: Compared to the control group (no β-blocker or digoxin), treatment with a β-blocker (RR, 0.58; P=0.005) or digoxin plus beta-blockers (RR, 0.59; P=0.008) was associated with a lower risk of death. Treatment with digoxin alone was not associated with a better survival. There was a similar reduction in mortality when considered separately: heart failure patients with atrial fibrillation, association or not with coronary artery disease, and heart failure with decreased or preserved systolic function.

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vs digoxin plus beta-blockers vs No digoxin or beta-blockers (control group)	2004 were retroactively identified and followed until September 2007			The initial multivariate model was constructed using the predictors of all cause mortality as potential confounders. After adjustment, treatment with β-blocker alone or in combination with digoxin remained significantly associated with a better survival (RR, 0.618; P=0.04 and RR, 0.543; P=0.01, respectively). A stepwise selection technique was used to determine the final model, which included four factors associated with mortality: older age (P<0.001), decreased left ventricular ejection fraction (P=0.001), chronic renal insufficiency (P=0.007), and lack of treatment with beta-blockers alone or in combination with digoxin was associated with better survival (RR, 0.618; P=0.04 and RR, 0.543; P=0.01). Secondary: Not reported
Friberg et al.[40] (2009) Digoxin vs no digoxin	COHORT, OB Individuals treated as inpatients or outpatients for AF or atrial flutter	N=2,824 4.6 years (mean duration)	Primary: Mortality Secondary: Rates of hospitalization for heart failure, number of days at hospital for any cause, frequency of MI, frequency of ischemic stroke, and rate of pacemaker implantations	Primary: In the unadjusted analysis, 1,038 patients died; 412 were prescribed digoxin at index and 626 did not receive digoxin. The mortality rate was higher among individuals who were treated with digoxin (51 vs 31%; P<0.001; HR, 1.94; 95% CI, 1.71 to 2.20). When adjusted for age, gender, comorbidities and medications, the difference in mortality was not significant (HR, 1.10; 95% CI, 0.94 to 1.28). The relationship between mortality and digoxin treatment at the latest, rather than the first, contact during the observation period was also studied. Unadjusted mortality was higher among patients treated with digoxin (48 vs 31%, P<0.001); However, after multivariable adjustment, there was no difference (HR, 1.05; 95% CI, 0.92 to 1.20). When patients were matched according to their individual propensity scores, there was no difference in mortality related to digoxin use (HR, 1.05; 95% CI, 0.90 to 1.23). Secondary: Individuals treated with digoxin, who had high propensity scores for this treatment, were less often hospitalized for heart failure. The number of days in the hospital for any cause did not differ between groups. There was no difference in the frequency of myocardial infarctions or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ischemic strokes related to digoxin use. There was an increased rate of pacemaker implantations among patients with digoxin as compared to those without digoxin (HR, 1.99; 95% CI, 1.16 to 3.43).
Georgiopoulou et al.[41] (2009) Digoxin (median daily dose of 0.13 mg/day) vs no digoxin	COHORT, RETRO Patients 18 to 70 years of age with advanced heart failure, LVEF ≤30% on maximum tolerated medical therapy, and NYHA Class II to IV	N=455 27 months (median duration)	Primary: Time to death, urgent transplantation, or left ventricular assist device implantation Secondary: Composite of the primary outcome plus hospitalization for heart failure, all-cause hospitalizations, and heart failure-related hospitalizations	Primary: Death, urgent transplantation, or left ventricular assist device implantation occurred in 36.6% of patients on digoxin compared to 15.8% of patients not receiving digoxin (HR, 2.28; 95% CI, 1.51 to 3.43; P<0.001). Secondary: The composite of primary outcome plus heart failure hospitalization occurred in 63.0% of patients on digoxin compared to 40.4% of patients not receiving digoxin (HR, 1.71; 95% CI, 1.32 to 2.23; P<0.001). All-cause hospitalization rates (HR, 1.58; 95% CI, 1.18 to 2.13; P<0.01) and heart failure-related hospitalization rates (HR, 1.81; 95% CI, 1.17 to 2.80; P<0.05) were higher in patients taking digoxin compared to those who were not taking digoxin.
Butler et al.[42] (2010) Val-HeFT Digoxin vs no digoxin The analyses of this trial were carried out in patient groups based on digoxin use at baseline.	Post-hoc analysis of Val-HeFT (DB, PC, MC, RCT) Patients with symptomatic heart failure	N=5,010 (n=3,374 digoxin-treated patients, n=1,636 patients not receiving digoxin) 23 months (mean duration)	Primary: All-cause mortality, first morbid event, heart failure hospitalizations Secondary: Not reported	Primary: Risk of death (n=3,249; HR, 1.28; 95% CI, 1.05 to 1.57; P=0.02), first morbid event (n=3,249; HR, 1.35; 95% CI, 1.15 to 1.59; P<0.001), first hospitalization for heart failure (n=3,249; HR, 1.41; 95% CI, 1.12 to 1.78; P=0.004), and sudden deaths (n=3,067; HR, 1.36; 95% CI, 1.04 to 1.78; P=0.03), but not pump failure deaths (n=2,875; HR, 1.48; 95% CI, 0.95 to 2.30; P=0.08), remained were significantly higher among patients receiving baseline digoxin compared to those were not. Secondary: Not reported

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>Lam et al.[43] (2018)

Digoxin

vs

no digoxin (matched cohort)</td><td>COHORT, RETRO

Hospitalized Medicare beneficiaries with HFrEF (EF <45%) receiving β-blockers</td><td>N=334

30 days</td><td>Primary:
All-cause readmission

Secondary:
HF readmission, all-cause mortality, and the composite endpoint of all-cause readmission or all-cause mortality</td><td>Primary:
All-cause readmission occurred in 15% and 27% of matched patients receiving and not receiving a new discharge prescription for digoxin, respectively (HR when digoxin use is compared with no digoxin use: 0.51, 95% CI, 0.31 to 0.83; P=0.007).

Secondary:
<table><tr><th></th><th>No digoxin</th><th>Digoxin</th><th>HR (95% CI)</th><th>P-value</th></tr><tr><td>HR readmission</td><td>11%</td><td>5%</td><td>0.48 (0.22 to 1.07)</td><td>0.071</td></tr><tr><td>All-cause mortality</td><td>3%</td><td>2%</td><td>0.80 (0.22 to 2.99)</td><td>0.742</td></tr><tr><td>Composite</td><td>29%</td><td>17%</td><td>0.54 (0.34 to 0.86)</td><td>0.009</td></tr></table></td></tr>
<tr><td>Siu et al.[44] (2009)

Digoxin IV 0.5 mg bolus dose, followed by 0.25 mg every 8 hours

vs

diltiazem IV 0.25 mg/kg bolus injection over 2 minutes, followed by a second bolus of 0.35 mg/kg if ventricular rate remained >90 bpm 15 minutes later, and then a maintenance infusion at 10 mg/hr for 24 hours</td><td>OL, RCT

Patients who presented to the Emergency Department with symptomatic acute AF for <48 hours and rapid ventricular rate >120 bpm requiring hospitalization</td><td>N=150

3 years</td><td>Primary:
Sustained ventricular rate control (<90 bpm) within 24 hours

Secondary:
Time to ventricular rate control, sinus rhythm conversion, symptom severity, hospital stay, and adverse drug events</td><td>Primary:
After the initial 24 hours, ventricular rate control was achieved in 119 of 150 patients (79%).

Secondary:
The median time to ventricular rate control in patients assigned to the diltiazem regimen was three hours (range: 1 to 21 hours) and was noticeably shorter than that of digoxin (six hours, 3 to 15 hours) and amiodarone (seven hours, 1 to 18 hours) based on the log-rank test (P<0.0001). Among the patients, 45 assigned to diltiazem achieved ventricular rate control (90%), which was significantly more than among those assigned to digoxin (74%; P=0.047) and amiodarone (74%; P=0.047). Patients assigned to diltiazem had persistently the lowest mean ventricular rate after the first hour of drug administration compared to the other two groups (P<0.05).

Sinus rhythm conversion rate was 31% within the first 24 hours and 38% upon discharge. There was no significant difference in sinus rhythm conversion rate among the diltiazem regimen, digoxin regimen, and amiodarone regimen within the first 24 hours (34 vs 24 vs 36%; P>0.05) and on discharge (42 vs 28 vs 44%; P>0.05). There were no differences among the three groups in the median time to sinus conversion: five hours (1 to 16 hours), six hours (1 to 19 hours), and seven hours (1 to 17 hours), respectively (P>0.05).</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amiodarone IV loading infusion of 300 mg over the first hour, followed by 10 mg/kg over 24 hours				Patients receiving diltiazem had lower AF symptom severity scores at 24 hours compared to digoxin (P=0.047) and amiodarone (P=0.01). There was no significant difference in AF symptom frequency scores at 24 hours among the three groups. At 24 hours, patients receiving diltiazem had the greatest reduction in both AF symptom frequency score (12.7; P=0.001) and severity score (9.8; P<0.0001) compared to those who received digoxin (8.6 and 6.1) or amiodarone (9.0 and 6.1). Patients who achieved spontaneous sinus conversion had the greatest reduction in AF symptom frequency score and severity score (17.2 and 11.0, respectively) compared to those who achieved ventricular rate control (9.4 and 7.7) or failed ventricular rate control (1.2 and 0.1; all, P<0.001). Among patients who remained in AF, those receiving diltiazem had the greatest reduction in both AF symptom frequency score (9.0) and severity score (7.8) in comparison with patients receiving digoxin (6.3 and 5.3; P=0.049), and patients receiving amiodarone (5.6 and 3.3; P<0.01). The mean hospital stay was 4.4 days. There was a significantly shorter hospital stay (P=0.023) in the diltiazem group (3.9 days) compared to the digoxin (4.7 days) and amiodarone groups (4.7 days). Only one patient who received amiodarone demonstrated a major adverse event with phlebitis at the intravenous access site requiring prolonged hospitalization. No bradycardia, hypotension, new-onset CHF, or MI was observed in any of the patients.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, NI=noninferiority, OB=observational, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, XO=cross-over
Miscellaneous abbreviations: ACE inhibitor=angiotensin-converting enzyme inhibitor, AF=atrial fibrillation, AMI=acute myocardial infarction, BP=blood pressure, CHF=congestive heart failure, CI=confidence interval, CV=cardiovascular, ECG=electrocardiogram, ECV=electrical cardioversions, HR=heart rate, INR=international normalized ratio, LVED=left ventricular end-diastolic, LVEF=left ventricular ejection fraction, MET=mean exercise tolerance, MFI-20=Multidimensional Fatigue Inventory-20, MI=myocardial infarction, MLHF=Minnesota Living with Heart Failure, NNH=number needed to harm, NNT=number needed to treat, NYHA=New York Heart Association, OR=odds ratio, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, SDC=serum digoxin concentration, SF-36=Short Form Health Survey

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 Cardiotonic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Digoxin	injection, solution, tablet	Lanoxin®*, Lanoxin Pediatric®	$$$$$	$

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

X. Conclusions

Digoxin is the only cardiotonic agent that is currently available. It is an effective treatment option for heart failure due to its positive inotropic and neurohormonal deactivating effects. It is also beneficial for atrial arrhythmias due to its vagomimetic actions. Digoxin injection, solution, and tablets are all available in a generic formulation. Although there are minor differences with respect to pharmacokinetic parameters, all digoxin products are equally effective. Due to its potential for drug interactions and other toxicities, digoxin therapy should be monitored closely.[1-3,10]

There are several guidelines that discuss the role of digoxin for the treatment of atrial fibrillation and heart failure. Digoxin slows atrioventricular conduction more effectively at rest than during exercise, but does not block exercise-induced tachycardia, which limits its use. For the treatment of atrial fibrillation, β-blockers and nondihydropyridine calcium channel antagonists are recommended as initial therapy to control heart rate.[4,5] Digoxin can effectively control heart rate at rest, but it is ineffective at controlling the ventricular response during exercise.[4] A combination of digoxin and either a β-blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise.[4,5] Studies finding an association between

digoxin therapy and mortality raise concerns about its use, particularly long term.[4] In the AFFIRM trial, digoxin was associated with an increase in mortality, which in a post hoc analysis was found to be irrespective of sex or heart failure.[19] Arrhythmias, which are dose related, are a potential source of mortality; in the DIG trial, serum levels >0.9 ng/mL were associated with increased mortality.[4,30] However, in another AFFIRM subgroup propensity-matched analysis with paroxysmal and persistent AF, there was no increase in mortality or hospitalization in those taking digoxin as baseline initial therapy.[18] Digoxin should not be used for the pharmacologic cardioversion of atrial fibrillation. It has not been proven to be effective in preventing postoperative atrial fibrillation and is not recommended in this setting.[4-6] For the treatment of heart failure, angiotensin converting enzyme inhibitors, β-blockers, and diuretics are the cornerstones of therapy. Digoxin may be considered for patients with systolic dysfunction who have signs/symptoms of heart failure while receiving standard therapy. It has been shown to improve symptoms, exercise tolerance, and quality of life and decrease hospitalizations for heart failure; however, it has no effect on survival. Digoxin is not useful for the acute management of decompensated heart failure.[7-9] The available guidelines do not give preference to one particular digoxin formulation over another.[4-9]

Therefore, all brand cardiotonic agents 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 cardiotonic agent 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cardiac Drugs, Miscellaneous
AHFS Class 240492
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I. Overview

Angina occurs when myocardial oxygen demand exceeds supply, which results in chest discomfort or pain. Common treatments for chronic angina include nitrates, β-blockers, and calcium channel blockers.[1] Ranolazine is approved for the treatment of chronic angina. It may be used in combination with β-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid lowering therapy, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers. The exact mechanism of ranolazine is unknown. The anti-ischemic and antianginal effects do not depend upon reductions in heart rate or blood pressure.[2]

Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35%, who are in sinus rhythm with resting heart rate ≥70 beats per minute and either are on maximally tolerated doses of β-blockers or have a contraindication to β-blocker use. It has also been approved for the treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients aged six months and older, who are in sinus rhythm with an elevated heart rate. Ivabradine reduces sinus rate by blocking the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker I_f current, which regulates heart rate.[3,4]

Tafamidis (Vyndaqel® and Vyndamax®) is a transthyretin (TTR) stabilizer indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.[5] Tafamidis binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.[5] Cardiac amyloidosis is characterized by myocardial accumulation of misfolded protein fragments that form insoluble amyloid fibrils leading to progressive cardiac damage and impaired cardiac function.[6,7] There are two main subtypes of ATTR-CM: (1) hereditary ATTR (hATTR) amyloidosis, resulting from mutations in the TTR gene (also known as ATTR mutant); and (2) wild type (ATTRwt) amyloidosis (previously known as senile systemic amyloidosis), resulting from misfolded native or nonmutant TTR and associated with aging.[6,7] Tafamidis is the first disease-modifying drug FDA-approved for ATTR-CM.[5] The management of ATTR-CM has otherwise focused on symptomatic treatment of heart failure symptoms and/or heart transplantation.[7]

Mavacamten (Camzyos®) is an allosteric and reversible inhibitor selective for cardiac myosin indicated for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.[8] Mavacamten modulates the number of myosin heads that can enter "on actin" (power-generating) states, which will reduce the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation.[8] Mechanistic hallmark signs of HCM include excess myosin actin cross-bridge formation and dysregulation of the super-relaxed state.[8] In patients with HCM, mavacamten inhibits myosin, thus reducing dynamic left ventricular outflow tract (LVOT) obstruction and improves cardiac filling pressures.[8]

The miscellaneous cardiac drugs that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ranolazine is available in a generic formulation. This class was last reviewed in February 2022.

Table 1. Cardiac Drugs, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ivabradine	tablet, solution	Corlanor®	none
Mavacamten	capsule	Camzyos®	none
Ranolazine	extended-release tablet, extended-release granules	Aspruzyo Sprinkle® ER, Ranexa®*	ranolazine

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Tafamidis	capsule	Vyndamax®, Vyndaqel®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous cardiac drugs are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cardiac Drugs, Miscellaneous

Clinical Guideline	Recommendations
American Heart Association/American College of Cardiology/American College of Clinical Pharmacy/American Society for Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With Chronic Coronary Disease (2023)**[9]	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for six months post PCI followed by single

Clinical Guideline	Recommendations
	antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a one- to three-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to three years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. • In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. • In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%,

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	the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.

European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)**[10]	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u>
	• The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events.
	• Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.
	• It is recommended to educate patients about the disease, risk factors and treatment strategy.
	• It is indicated to review the patient's response soon after starting therapy.
	• Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding.
	• Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended
	• ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events
	• Angina/ischemia relief:
	  ○ Short-acting nitrates are recommended.
	  ○ First-line treatment is indicated with ß-blockers and/or calcium channel

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	blockers to control heart rate and symptoms. o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. • Event prevention: o Low-dose aspirin daily is recommended in all stable CAD patients. o Clopidogrel is indicated as an alternative in case of aspirin intolerance. o Statins are recommended in all stable CAD patients. o It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes). <u>Treatment in patients with microvascular angina</u> • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • ß-blockers are recommended as a first-line treatment. • Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT). • Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only. • Platelet function testing or genetic testing may be considered in specific or high-risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low-risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation

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	of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low. • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months. <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk. • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
American College of Cardiology Foundation/ American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[11]**	<u>Early hospital care- standard medical therapies</u> • Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. • Anti-ischemic and analgesic medications o Nitrates ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2)

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	evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue beta-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to beta-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of beta-clockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when beta-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should

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	be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents

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	○ Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. ○ In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. ○ In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. ○ In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge ○ Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. ○ All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. ○ Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. ○ Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. ○ For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. ○ If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. ○ Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy ○ Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. ○ In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. ○ In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS ○ The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. ○ Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
European Society of	<u>Pharmacological treatment of ischemia</u>

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Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2020)[12]**	• Sublingual or intravenous nitrates and early initiation of beta-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications.
	• Continuation of chronic beta-blocker therapy is recommended unless the patient is in overt heart failure
	• Sublingual or intravenous nitrates are recommended to relieve angina; intravenous treatment is recommended in patients with recurrent angina, uncontrolled hypertension, or signs of heart failure.
	• In patients with suspected/confirmed vasospastic angina, calcium channel blockers, and nitrates should be considered and beta-blockers avoided.
	
	<u>Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes</u>
	• Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150 to 300 mg (in aspirin-naïve patients) and a maintenance dose of 75 to 100 mg/day long-term regardless of treatment strategy.
	• A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risks of bleeds.
	  ○ Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindication, for all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).
	  ○ Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. Prasugrel should be considered in preference to ticagrelor in NSTE-ACS patients who proceed to PCI.
	  ○ Clopidogrel (300 to 600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.
	• $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after DES implantation may be considered in patients deemed at high bleeding risk.
	• Pre-treatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy.
	• It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known.
	• It is not recommended to administer prasugrel in patients whom coronary anatomy is not known.
	• GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.
	• Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI.
	• It is not recommended to administer GPIIb/IIIa inhibitors in patients whom coronary anatomy is not known.
	• $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of the ischemic and bleeding risks of the patient.
	
	<u>Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes</u>
	• Parenteral anticoagulation is recommended at the time of diagnosis according to both ischemic and bleeding risks.
	• Fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy.
	• Bivalirudin is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI.
	• UFH is recommended in patients undergoing PCI who did not receive any

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	anticoagulant. • In patients on fondaparinux undergoing PCI, a single intravenous bolus of UFH is recommended during the procedure. • Enoxaparin or UFH are recommended when fondaparinux is not available. • Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated for PCI with subcutaneous enoxaparin. • Additional activated clotting time-guided intravenous boluses of UFH during PCI may be considered following initial UFH treatment. • Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated. • Crossover between UFH and LMWH is not recommended. • In NSTEMI patients with no prior stroke/TIA and at high ischemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation. <u>Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation</u> • In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a $CHADS_2$-VASc score ≥2, recent VTE, mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. • An early invasive coronary angiography (within 24 hours) should be considered in moderate- to high-risk patients, irrespective of oral anticoagulant exposure, to expedite treatment allocation (medical vs PCI vs CABG) and to determine optimal antithrombotic regimen. • Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to oral anticoagulation before coronary angiography is not recommended. • During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all non-vitamin K antagonist oral anticoagulants (NOACs) and if INR is <2.5 in VKA-treated patients. • Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. • Periprocedural DAPT administration consisting of aspirin and clopidogrel up to one week is recommended • Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months • Following coronary stenting, dual (oral) antiplatelet therapy (DAPT) including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with non-ST-elevation acute coronary syndromes and atrial fibrillation with a $CHADS_2$-VASc score of 1 (in males) or 2 (in females). • If at low bleeding risk (HAS-BLED ≤2), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for six months, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months. • If at high bleeding risk (HAS-BLED ≥3), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for one month, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months irrespective of the stent type. • Dual therapy with oral anticoagulant and clopidogrel may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis). • The use of ticagrelor or prasugrel as part of triple therapy is not recommended. • In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year. <u>Recommendations for post-interventional and maintenance treatment</u>

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	• In patients with NSTE-ACS with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding. • Adding a second anti-thrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a moderate to high risk of ischemic events and without increased risk of major bleeding. • After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after three months should be considered • After stent implantation in patients undergoing DAPT, stopping aspirin after three to six months should be considered, depending on balance between ischemic and bleeding risk. • De-escalation of $P2Y_{12}$ inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **Guideline for the Management of Heart Failure (2022)**[11]	Treatment of Stage A heart failure (HF) • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF.(LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) Treatment of Stage B heart failure • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF) • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B)

Clinical Guideline	Recommendations
	• For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may

Clinical Guideline	Recommendations
	increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as “bridge therapy” in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory

Clinical Guideline	Recommendations
	support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B) Treatment of Transthyretin Cardiac Amyloidosis • In select patients with wild-type or variant trans-thyretin cardiac amyloidosis and NYHA class I to III HF symptoms, transthyretin tetramer stabilizer therapy (tafamidis) is indicated to reduce cardiovascular morbidity and mortality. • At 2020 list prices, tafamidis provides low economic value (>$180 000 per QALY gained) in patients with HF with wild-type or variant transthyretin cardiac amyloidosis. • In patients with cardiac amyloidosis and AF, anticoagulation is reasonable to reduce the risk of stroke regardless of the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category) score.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[14]	Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a beta-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an

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	MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a beta-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk • of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF

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	admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.

National Institute for Health and Clinical Excellence: **Chronic heart failure in adults: management (2018)**[15]	<u>Treating heart failure with reduced ejection fraction</u>
	• First-line treatment
	  ○ Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have heart failure with reduced ejection fraction.
	• ACE inhibitors
	  ○ Do not offer ACE inhibitor therapy if there is a clinical suspicion of hemodynamically significant valve disease until the valve disease has been assessed by a specialist.
	  ○ Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every two weeks) until the target or maximum tolerated dose is reached.
	  ○ Measure serum sodium and potassium, and assess renal function, before and one to two weeks after starting an ACE inhibitor, and after each dose increment.
	  ○ Measure blood pressure before and after each dose increment of an ACE inhibitor.
	  ○ Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell.
	• Alternative treatments if ACE inhibitors are not tolerated
	  ○ Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side effects with ACE inhibitors.
	  ○ Measure serum sodium and potassium, and assess renal function, before and after starting an ARB and after each dose increment.
	  ○ Measure blood pressure after each dose increment of an ARB.
	  ○ Once the target or maximum tolerated dose of an ARB is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell.
	  ○ If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have heart failure with reduced ejection fraction.
	• Beta-blockers
	  ○ Do not withhold treatment with a beta-blocker solely because of age or the

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	presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. o Introduce beta-blockers in a 'start low, go slow' manner. Assess heart rate and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. o Switch people whose condition is stable and who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. • Mineralocorticoid receptor antagonists (MRAs) o Offer an MRA, in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. o Measure serum sodium and potassium, and assess renal function, before and after starting an MRA and after each dose increment. o Measure blood pressure before and after each dose increment of an MRA. o Once the target, or maximum tolerated, dose of an MRA is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell. • Specialist treatment o Ivabradine is recommended as an option for treating chronic heart failure for people: ▪ with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and ▪ who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and ▪ who are given ivabradine in combination with standard therapy including beta-blocker therapy, ACE inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and ▪ with a left ventricular ejection fraction of 35% or less. o Ivabradine should only be initiated after a stabilization period of four weeks on optimized standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. o Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. o Sacubitril-valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: ▪ with New York Heart Association (NYHA) class II to IV symptoms and ▪ with a left ventricular ejection fraction of 35% or less and ▪ who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or ARBs. o Treatment with sacubitril-valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. o Hydralazine in combination with nitrate ▪ Seek specialist advice and consider offering hydralazine in combination with nitrate (especially if the person is of African or Caribbean family origin and has moderate to severe heart failure [NYHA class III/IV] with reduced ejection fraction). o Digoxin ▪ Digoxin is recommended for worsening or severe heart failure with reduced ejection fraction despite first-line treatment for heart failure. Seek specialist advice before initiating.

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	▪ Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within eight to 12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence. ▪ The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. <u>Treating heart failure with reduced ejection fraction in people with chronic kidney disease</u> • For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR of 30 ml/min/1.73 m^2 or above: o offer the treatment outlined above and o if the person's eGFR is 45 ml/min/1.73 m^2 or below, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, MRAs and digoxin. • For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR below 30 ml/min/1.73 m^2, the specialist heart failure multidisciplinary team should consider liaising with a renal physician. • Monitor the response to titration of medicines closely in people who have heart failure with reduced ejection fraction and chronic kidney disease, taking into account the increased risk of hyperkalemia. <u>Managing all types of heart failure: Pharmacological treatment</u> • Diuretics o Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. o People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice. • Calcium-channel blockers o Avoid verapamil, diltiazem and short-acting dihydropyridine agents in people who have heart failure with reduced ejection fraction. • Amiodarone o Make the decision to prescribe amiodarone in consultation with a specialist. o Review the need to continue the amiodarone prescription at the six-monthly clinical review. o Offer people taking amiodarone liver and thyroid function tests, and a review of side effects, as part of their routine 6-monthly clinical review. • Anticoagulants o For people who have heart failure and atrial fibrillation, follow the recommendations on anticoagulation in the NICE guideline on atrial fibrillation. Be aware of the effects of impaired renal and liver function on anticoagulant therapies. o In people with heart failure in sinus rhythm, anticoagulation should be considered for those with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus. • Vaccinations o Offer people with heart failure an annual vaccination against influenza. o Offer people with heart failure vaccination against pneumococcal disease (only required once). • Contraception and pregnancy o In women of childbearing potential who have heart failure, contraception

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	and pregnancy should be discussed. If pregnancy is being considered or occurs, specialist advice should be sought. Subsequently, specialist care should be shared between the cardiologist and obstetrician.
Orphanet Journal of Rare Diseases: **Guideline of transthyretin-related hereditary amyloidosis for clinicians (2013)[16]**	• Some mutations induce cardiomyopathy as the predominant feature (e.g., Val122Ile, Ile68Leu, Thr60Ala, Leu111Met) while others are associated primarily with neuropathy (e.g., Val30Met) • The clinical spectrum of cardiovascular involvement ranges from asymptomatic AV and bundle branch block to severe, rapidly progressive heart failure • To confirm amyloidosis, tissue biopsy is recommended and immunolabeling can identify TTR amyloidosis, but cannot distinguish wild-type from hereditary forms. • Current techniques for performing sequence analysis of TTR, the only gene known to be associated with TTR amyloidosis, detect >99% of disease-causing mutations. • The main indication for combined heart and liver transplant is severe heart failure due to amyloidotic cardiomyopathy in a patient without advanced neurologic involvement. • In a cardiopathy study, patients with wild-type or Val122Ile TTR amyloidosis received tafamidis and compared with historical controls, patients receiving tafamidis experienced smaller changes from baseline in NT-proBNP and 6MWT measures and a lower incidence of cardiovascular hospitalization/death at 12 months.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous cardiac drugs 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 Cardiac Drugs, Miscellaneous[2,3,5,8]

Indication	Ivabradine	Mavacamten	Ranolazine	Tafamidis
Treatment of adults with symptomatic New York Heart Association class II to III obstructive hypertrophic cardiomyopathy to improve functional capacity and symptoms		✔		
Treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization				✔
Treatment of chronic angina			✔	
Treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients aged six months and older, who are in sinus rhythm with an elevated heart rate	✔			
Reduction in the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm	✔			

Indication	Ivabradine	Mavacamten	Ranolazine	Tafamidis
with resting heart rate ≥70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use				

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous cardiac drugs are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cardiac Drugs, Miscellaneous[17]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ivabradine	40	70	Intestines (extensive, % not reported) Liver (extensive, % not reported)	Renal and Feces (% not reported)	6
Mavacamten	85	97 to 98	Liver (extensive, % not reported)	Renal (85) Feces (7)	144 to 216
Ranolazine	55	62	Intestines (rapid and extensive, % not reported) Liver (rapid and extensive, % not reported)	Renal (75) Feces (25)	7.0 to 8.9
Tafamidis	Not reported	>99	Not fully characterized; glucuronidation observed	Renal (22) Feces (59)	49

V. Drug Interactions

Major drug interactions with the miscellaneous cardiac drugs are listed in Table 5.

Table 5. Major Drug Interactions with the Cardiac Drugs, Miscellaneous[17]

Generic Name(s)	Interaction	Mechanism
Ivabradine	CYP3A4 Inhibitors	Concurrent use of ivabradine and CYP3A4 inhibitors may result in increased exposure of ivabradine.
Ivabradine	CYP3A4 Inducers	Concurrent use of ivabradine and CYP3A4 inducers may result in decreased exposure of ivabradine.
Ivabradine	QT Interval Prolonging Drugs	Concurrent use of ivabradine and QT interval prolonging drugs may result in increased risk of QT prolongation.
Ivabradine	Diltiazem, Verapamil	Concurrent use may result in increased exposure of ivabradine, increased risk for exacerbation of bradycardia, and increased risk of conduction disturbances.
Ivabradine	Conivaptan	Concurrent use of conivaptan and ivabradine may result in increased ivabradine exposure.
Ivabradine	Fluconazole	Concurrent use of fluconazole and ivabradine may result in increased ivabradine exposure and risk for QT interval prolongation.
Ivabradine	Fosphenytoin	Concurrent use of fosphenytoin and ivabradine may result in decreased exposure of ivabradine and increased risk of QT prolongation.
Mavacamten	Moderate to strong CYP2C19 inhibitor	Concurrent use of mavacamten and moderate to strong CYP2C19 inhibitors increase mavacamten exposure, which may lead to an increased risk of heart failure due to systolic dysfunction.
Mavacamten	Strong CYP3A4 inhibitors	Concurrent use of mavacamten and strong CYP3A4 inhibitors increase mavacamten exposure, which may lead to an increased

Generic Name(s)	Interaction	Mechanism
		risk of heart failure due to systolic dysfunction.
Mavacamten	Moderate to strong CYP2C19 inducer	Concurrent use of mavacamten and strong CYP2C19 inducers decrease mavacamten exposure, which will reduce the efficacy of mavacamten
Mavacamten	Strong CYP3A4 inducers	Concurrent use of mavacamten and strong CYP3A4 inducers decrease mavacamten exposure, which will reduce the efficacy of mavacamten
Mavacamten	Hormonal contraceptives	Concurrent use of mavacamten and progestin and ethinyl estradiol may decrease exposures of ethinyl estradiol and progestin, which can lead to contraceptive failure or an increase in breakthrough bleeding.
Mavacamten	Omeprazole	Omeprazole increases mavacamten AUC, thus increasing clearance and decreasing plasma drug concentration.
Mavacamten	Verapamil SR, disopyramide, ranolazine with a beta blocker	Concurrent use of mavacamten and medications that reduce cardiac contractility can cause negative additional negative inotropic effects of mavacamten.
Mavacamten	Ketoconazole	Ketoconazole increases mavacamten AUC, thus increasing clearance and decreasing plasma drug concentration.
Ranolazine	Azole antifungals	Certain azole antifungals inhibit the metabolism of ranolazine, increasing plasma concentrations of ranolazine and the risk of toxicity.
Ranolazine	Colchicine	Use of P-glycoprotein/ABCB1 inhibitors with colchicine may increase the serum concentration of colchicine. Colchicine distribution into certain tissues (e.g., brain) may also be increased.
Ranolazine	CYP3A4 Inhibitors	Concurrent use of ranolazine and CYP3A4 inhibitors may result in increased exposure of ranolazine and increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Ranolazine	CYP3A4 Inducers	Concurrent use of ranolazine and CYP3A4 inducers may result in decreased exposure of ranolazine.
Ranolazine	HMG-CoA reductase inhibitors	Ranolazine inhibits the metabolism of certain HMG-CoA reductase inhibitors, increasing plasma concentrations of HMG-CoA reductase inhibitors and the risk of adverse reactions.
Ranolazine	Macrolides and related antibiotics	Macrolide antibiotics inhibit the metabolism of ranolazine by the cytochrome P450 (CYP) 3A system. Concomitant use may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	Nefazodone	Plasma concentrations and pharmacologic effects of ranolazine may be increased by coadministration of nefazodone. Inhibition of cytochrome P4503A4 by nefazodone may decrease the metabolic elimination of ranolazine.
Ranolazine	Protease inhibitors	Protease inhibitors inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	QT Interval Prolonging Drugs	Concurrent use of ranolazine and QT interval prolonging drugs may result in increased risk of QT prolongation.
Ranolazine	Thioridazine	Concurrent use of CYP2D6 inhibitors with thioridazine may increase serum concentrations of thioridazine, increasing the risk of QT interval prolongation and arrhythmias.
Ranolazine	Aprepitant	Plasma concentrations and pharmacologic effects of ranolazine may be increased by coadministration of aprepitant. Inhibition of CYP3A4 by aprepitant may decrease the metabolic elimination of ranolazine.
Ranolazine	Barbiturates	Pharmacologic effects and plasma concentrations of ranolazine

Generic Name(s)	Interaction	Mechanism
		may be decreased by barbiturates. Induction of CYP3A isoenzymes by barbiturates may increase the metabolic elimination of the ranolazine.
Ranolazine	Carbamazepine	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by carbamazepine. Induction of CYP3A isoenzymes by carbamazepine may increase the metabolic elimination of the ranolazine.
Ranolazine	Diltiazem	Diltiazem inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	Erythromycin	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by erythromycin. Induction of cytochrome P450 3A isoenzymes by erythromycin may increase the metabolic elimination of the ranolazine.
Ranolazine	Fluconazole	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by fluconazole. Induction of CYP3A isoenzymes by fluconazole may increase the metabolic elimination of the ranolazine.
Ranolazine	Hydantoins	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by hydantoins. Induction of CYP3A isoenzymes by hydantoins may increase the metabolic elimination of the ranolazine.
Ranolazine	Rifamycins	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by rifamycins. Induction of CYP3A isoenzymes by rifamycins may increase the metabolic elimination of the ranolazine.
Ranolazine	Verapamil	Verapamil inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Tafamidis	BCRP Substrates	Tafamidis inhibits breast cancer resistant protein (BCRP) in vitro and may increase exposure of substrates of this transporter (e.g., methotrexate, rosuvastatin, imatinib) following tafamidis administration.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous cardiac drugs are listed in Table 6. There are no adverse reactions listed in the manufacturer's labeling for tafamidis.[5]

Table 6. Adverse Drug Events (%) Reported with the Cardiac Drugs, Miscellaneous[18]

Adverse Events	Ivabradine	Mavacamten	Ranolazine	Tafamidis
Cardiovascular				
Atrial fibrillation	8	-	-	-
Bradycardia	4 to 10	-	≤ 4.0	-
Decreased left ventricular ejection fraction	-	6	-	-
Heart block	✔	-	-	-
Hypertension	9	-	-	-
Hypotension	< 1	-	≤ 4.0	-
Orthostatic hypotension	-	-	≤ 4.0	-
Palpitation	-	-	≤ 4.0	-
Prolonged QT interval	-	-	✔	-
Sinoatrial arrest	✔	-	-	-
Syncope	< 1	6	≤ 4.0	-

Adverse Events	Ivabradine	Mavacamten	Ranolazine	Tafamidis
Torsades de Pointes	< 1	-	✔	-
Ventricular fibrillation	< 1	-	-	-
Ventricular tachycardia	< 1	-	-	-
Central Nervous System				
Ataxia	-	-	✔	-
Confusion	-	-	≤ 4.0	-
Dizziness	-	27	6	-
Hallucination	-	-	✔	-
Headache	-	-	6	-
Paresthesia	-	-	< 1	-
Phosphene	3	-	-	-
Tremor	-	-	< 1	-
Vertigo	< 1	-	≤ 4.0	-
Gastrointestinal				
Abdominal pain	-	-	≤ 4.0	-
Anorexia	-	-	≤ 4.0	-
Constipation	-	-	5	-
Diarrhea	-	-	-	✔
Dry mouth	-	-	≤ 4.0	-
Dyspepsia	-	-	≤ 4.0	-
Nausea	-	-	4	-
Vomiting	-	-	≤ 4.0	-
Genitourinary				
Dysuria	-	-	✔	-
Hematuria	-	-	≤ 4	-
Urine discoloration	-	-	< 1	-
Urinary retention	-	-	✔	-
Hematologic				
Eosinophilia	-	-	< 1	-
Leukopenia	-	-	< 1	-
Pancytopenia	-	-	< 1	-
Thrombocytopenia	-	-	< 1	-
Respiratory				
Dyspnea	-	-	≤ 4.0	-
Pulmonary fibrosis	-	-	< 1	-
Other				
Angioedema	< 1	-	< 1	-
Asthenia	-	-	≤ 4.0	-
Blurred vision	-	-	≤ 4.0	-
Diplopia	< 1	-	-	-
Erythema	< 1	-	-	-
Hyperhidrosis	-	-	≤ 4.0	-
Peripheral edema	-	-	≤ 4.0	-
Pruritus	< 1	-	-	-
Skin rash	< 1	-	✔	-
Tinnitus	-	-	≤ 4.0	-
Urticaria	< 1	-	-	-
Visual impairment	< 1	-	-	-

✔ Percent not specified.
- Event not reported.

Table 7. Boxed Warning for Mavacamten[8]

WARNING
RISK OF HEART FAILURE Mavacamten reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction. Echocardiogram assessments of LVEF are required prior to and during treatment. Initiation of mavacamten in patients with LVEF <55% is not recommended. Interrupt treatment if LVEF is <50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status. Concomitant use of mavacamten with certain cytochrome P450 inhibitors or discontinuation of certain cytochrome P450 inducers may increase the risk of heart failure due to systolic dysfunction; therefore, the use of mavacamten is contraindicated with the following: • Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors • Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers Because of the risk of heart failure due to systolic dysfunction, mavacamten is available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous cardiac drugs are listed in Table 8.

Table 8. Usual Dosing Regimens for the Cardiac Drugs, Miscellaneous[2,3,5,8,18]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ivabradine	To reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use: Tablet: 5 mg twice daily; after two weeks adjust dose based on resting heart rate to a maximum of 7.5 mg twice daily	The treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients aged six months and older, who are in sinus rhythm with an elevated heart rate: Oral solution, in patients weighing <40 kg: 0.05 mg/kg twice daily with food; after two weeks adjust dose based on resting heart rate to a maximum of 0.2 mg/kg twice daily for patients 6 months to <1 year of age and 0.3 mg/kg twice daily for patients ≥1 year of age, up to a total of 7.5 mg twice daily Tablet, in patients weighing ≥40 kg: 2.5 mg twice daily with food; after two weeks adjust dose based on resting heart rate to a maximum of 7.5 mg twice daily	Tablet: 5 mg 7.5 mg Solution: 5 mg/mL
Mavacamten	Treatment of adults with symptomatic New York Heart Association class II to III obstructive hypertrophic cardiomyopathy to improve functional capacity and symptoms: Capsule: initial, 5 mg once daily without regard to food; adjust dose	Safety and efficacy in pediatric patients have not been established.	Capsule: 2.5 mg 5 mg 10 mg 15 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	based on left ventricular ejection fraction and/or Valsalva left ventricular outflow tract gradient to a maximum of 15 mg once daily as detailed in the prescribing information		
Ranolazine	Treatment of chronic angina: Extended-release granule and tablet: initial, 500 mg twice daily; maximum: 1,000 mg twice daily	Safety and efficacy in children have not been established.	Extended-release tablet: 500 mg 1,000 mg Extended-release granules: 500 mg 1,000 mg
Tafamidis	Treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization: Capsule, Vyndaqel: 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily Capsule, Vyndamax: 61 mg (one 61-mg tafamidis capsules) orally once daily	Safety and efficacy in pediatric patients have not been established.	Capsule: 20 mg (tafamidis meglumine, Vyndaqel) 61 mg (tafamidis, Vyndamax)

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous cardiac drugs are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Cardiac Drugs, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Swedberg et al.[19] (2010) SHIFT Ivabradine 5 mg BID vs placebo Following the 14–day titration period, doses were either increased to 7.5 mg BID (or corresponding placebo) if resting HR was > 60 bpm; continued on 5 mg BID if resting HR was 50 to 60 bpm; or decreased to 2.5 mg BID if resting HR < 50 bpm or patient had signs or symptoms related to bradycardia.	DB, MC, PC, PG, RCT Patients ≥ 18 years of age with symptomatic systolic HF in sinus rhythm with resting heart rate ≥ 70 bpm, a LVEF ≤ 35%, receiving maximally tolerated doses of β-blockers and other guidelines-based HF therapies and hospitalized for HF within 12 months prior to study entry	N=6,558 22.9 months	Primary: Composite of CV death or hospital admission for worsening HF Secondary: Composite of CV death or hospital admission for worsening HF in patients receiving ≥ 50% of the target daily dose of a β -blocker (as defined by ESC guidelines) at randomization; all-cause death, any CV death; death from HF; all-cause admission to hospital; any CV admission and the composite of CV, hospital admission for worsening HF or hospital admission for non-fatal MI	Primary: Compared to placebo, ivabradine reduced the risk of the combined endpoint of hospitalization for worsening HF or CV death based on a time-to-event analysis (HR, 0.82; 95% CI, 0.75 to 0.90; P<0.0001). Secondary: The composite of CV death, or hospital admission for worsening HF or hospital admission for non-fatal MI was reduced for the ivabradine group compared to placebo (HR, 0.82; 95% CI, 0.74 to 0.89; P<0.0001). Hospital admissions for worsening HF occurred in 672 (21%) of patients on placebo versus 514 (16%) of those on ivabradine (HR, 0.74; 95% CI, 0.66 to 0.83; P<0.0001). All cause hospital admission was reduced in the ivabradine group compared to placebo (HR, 0.89; 95% CI, 0.82 to 0.96; P=0.003). Any CV hospital admission was also reduced in the ivabradine group compared to placebo (HR, 0.85; 95% CI, 0.78 to 0.92; P=0.0002). CV mortality was not significantly reduced in ivabradine group (P=0.128), but deaths due to HF did fall significantly (HR, 0.74; 95% CI, 0.58 to 0.94; P=0.014). Serious adverse events occurred at a lower rate in ivabradine group than in placebo (P=0.025). The incidence of symptomatic and asymptomatic bradycardia was more frequent in ivabradine group than in patients taking placebo (both P<0.0001). Reported visual symptoms occurred in 89 (3%) of patients taking ivabradine compared to < 1% in those taking placebo (P<0.0001).
Fox et al.[20] (2008) BEAUTIFUL	DB, MC, PC, RCT Patients ≥ 55 years	N=10,917 Median	Primary: Composite of CV death or	Primary: There was no significant difference between the ivabradine- and placebo-treated patients in CV death or admission to hospital for MI or new-onset

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ivabradine 5 mg BID vs placebo Following the 14–day titration period, doses were increased to 7.5 mg BID if resting HR was ≥ 60 bpm; dose reduced from 7.5 mg to 5 mg BID if resting heart rate was < 50 bpm, or if they had signs or symptoms related to bradycardia; study drug was discontinued in patients given 5 mg BID if resting HR was < 50 bpm, or if they had signs or symptoms related to bradycardia.	of age (18 years of age if diabetic) with documented CAD, LVEF < 40%, end-diastolic short-axis internal dimension > 56 mm by echocardiography, in normal sinus rhythm with resting heart rate ≥ 60 bpm, stable angina and/or HF symptoms for ≥3 months, and receiving optimal conventional CV medication on appropriate and stable doses for ≥1 month	duration of follow-up was 19 months with a maximum of 35 months	hospitalization for acute MI or new onset or worsening HF Secondary: Composite of hospitalization for acute coronary syndrome, for new onset or worsening HF, or coronary revascularization; mortality due to coronary artery disease; all-cause mortality; the individual components of the composite primary and secondary endpoints	or worsening HF (HR, 1.00; 95% CI, 0.91 to 1.10; P=0.94). A total of 1,119 patients died during the study, 572 (10%) in the ivabradine group and 547 (10%) in the placebo group (HR, 1.04; 95% CI, 0.92 to 1.16; P=0.55). Secondary: Ivabradine reduced secondary endpoints of admission to hospital for fatal or non-fatal MI in a prespecified subgroup of individuals with HR of ≥ 70 bpm (HR, 0.64; 95% CI, 0.49 to 0.84; P=0.001) and coronary revascularization (HR, 0.70; 95% CI, 0.52 to 0.93; P=0.016). This was not seen in the total study population. There was no statistical significance seen with the ivabradine group compared to placebo for any of the mortality endpoints (all-cause death: HR, 1.04; 95% CI, 0.92 to 1.16; P=0.55; cardiovascular death: HR, 1.07; 95% CI, 0.94 to 1.22; P=0.32; cardiac death: HR, 0.89; 95% CI, 0.71 to 1.12; P=0.33).
Fox et al.[21] (2014) SIGNIFY Ivabradine 7.5 mg BID	DB, MC, PC, RCT Patients ≥ 55 years of age with documented and treated stable CAD	N=19,102 Median follow-up 27.8 months	Primary: Composite of death from CV causes or nonfatal MI Secondary:	Primary: There was no significant difference between the ivabradine group and the placebo group in the incidence of death from CV causes or nonfatal MI (6.8% and 6.4%, respectively; HR, 1.08; 95% CI, 0.96 to 1.20; P=0.20). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo ivabradine dose was titrated up to 10 mg BID or down to 5 mg BID to achieve a target HR of 55 to 60 bpm	with no evidence of clinical HF, in sinus rhythm with a resting HR of ≥ 70 bpm on two consecutive electrocardiographic readings and at least one major adverse prognostic factor, or two minor adverse prognostic factors or a LDL cholesterol level > 160 mg per deciliter		Death from CV causes, nonfatal MI and death from any cause	There was no significant difference between the ivabradine group and the placebo group in the incidence of death from CV causes (3.4% and 3.2%, respectively; HR, 1.10; 95% CI, 0.94 to 1.28; P=0.25), nonfatal MI (2.8% and 2.6%, respectively; HR, 1.06; 95% CI, 0.89 to 1.26; P=0.52) or death from any cause (5.1% and 4.8%, respectively; HR, 1.06; 95% CI, 0.94 to 1.21; P=0.35). The incidence of bradycardia was higher with ivabradine compared to placebo (18.0% vs 2.3%; P<0.001).
Olivotto et al.[22] (2020) EXPLORER-HCM Mavacamten 5 mg/day (initial dose) for 30 weeks vs. placebo for 30 weeks Study medication was administered in addition to standard therapy, except disopyramide. Mavacamten dose	DB, MC, PC, PG, RCT Adult patients with obstructive hypertrophic cardiomyopathy with a peak left ventricular outflow tract (LVOT) gradient of 50 mmHg or greater at rest, left ventricular ejection fraction of at least 55%, and NYHA class II to III symptoms	N=251 1 year	Primary: 1.5 mL/kg/min or greater increase in peak oxygen consumption (pVO_2) and at least one NYHA class reduction, or a 3.0 mL/kg/min or greater pVO_2 increase without NYHA class worsening Secondary: Changes in post-exercise LVOT gradient, pVO_2, NYHA class, Kansas City Cardiomyopathy Questionnaire –	Primary: Patients receiving mavacamten met the primary endpoint more frequently than those receiving placebo (45 of 123 [37%] vs 22 of 128 [17%] respectively; difference, 19.5%; 95% CI, 8.7 to 30.1; P=0.0005). Secondary: At week 30, patients receiving mavacamten displayed a significant improvement in all secondary endpoints compared with placebo. Patients on mavacamten had greater reductions in post-exercise LVOT gradient (-36 mmHg; 95% CI, -43.2 to -28.1; P<0.0001), greater increase in pVO2 (+1.4 mL/kg/min, 0.6 to 2.1; P=0.0006), and improved symptom scores (KCCQ-CSS +9.1, 5.5 to 12.7; HCMSQ-SoB -1.8, -2.4 to -1.2; P<0.0001). Patients in the mavacamten group also improved by at least one NYHA class more frequently compared to placebo (80 of 123 [65%] vs 40 of 128 [31%] respectively; 95% CI, 22.2 to 45.4; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adjustments occurred at weeks 8 and 14 based on a target reduction in peak left ventricular outflow tract (LVOT) gradient less than 30 mm Hg and a mavacamten plasma concentration between 350 ng/mL and 700 ng/mL. Individualized doses included 2.5, 5, 10, or 15 mg orally.			Clinical Summary Score (KCCQ-CCS), and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB)	
Desai et al.[23] (2022) VALOR-HCM Mavacamten 5 mg/day (initial dose) for 32 weeks vs. placebo Mavacamten doses were titrated every 4 weeks based on left ventricular ejection fraction and left ventricular	DB, MC, PC, XO, RCT Adult patients with obstructive hypertrophic cardiomyopathy on maximal tolerated medical therapy referred for septal reduction therapy (SRT) with left ventricular outflow tract gradient (LVOT) ≥50 mmHg at rest or provocation, and a documented left	N=108 32 weeks	Primary: Composite of patient decision to proceed with SRT or eligibility for SRT according to 2011 American College of Cardiology/ American Heart Association guidelines. Secondary: Changes from baseline in postexercise LVOT, NYHA	Primary: At week 32, six of 56 (10.7%) patients in the original mavacamten group and seven of 52 (13.5%) patients in the placebo cross-over group continued to meet guideline criteria for septal reduction therapy or elected to undergo the procedure. One hundred three of 108 (95%) patients decided to continue in the long-term extension of this study. Secondary: At week 32, patients randomized to the mavacamten group experienced a similar reduction in postexercise LVOT to the cross-over group after week 16 (33 mmHg; 95% CI, -53.4 to -30.1 vs 36.3 mmHg; (95% CI, -48.9 to -23.7, respectively). Patients in the mavacamten group experienced a similar frequency of improvements compared to the cross-over group after week 16 of at least one NYHA class (48 of 53 [90.6%] vs 35 of 50 [70.0%], respectively), or at least two NYHA classes (16 of 53 [30.2%] vs 12 of 50 [24.0%], respectively). Patients receiving mavacamten exhibited similar improvements in KCCQ-23-CSS compared to the cross-over group after week 16 (13.1; 95% CI, 9.2 to 17.1 vs 8.0; 95% CI, 3.2 to 12.8).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
outflow tract gradient. Patients originally randomized to placebo were crossed over to mavacamten 5 mg/day at week 16, and doses were adjusted every 4 weeks.	ventricular ejection fraction ≥60%		functional class, Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score (KCCQ-23-CSS), NT-proBNP, and cardiac troponin I. Safety outcomes included incidence of left ventricular ejection fraction <50%, hospitalization for heart failure, and atrial fibrillation or ventricular tachyarrhythmia	Patients receiving mavacamten also exhibited improvements in NT-proBNP (-417 ng/L; 95% CI, -706 to -186) and troponin I (-7.4 ng/L; 95% CI, -11.1 to -4.8). These improvements occurred similarly in patients in the cross-over group between weeks 16 and 32 in both NT-proBNP (-451 ng/L; 95% CI, -581 to -298) and troponin I (-6.8 ng/L; 95% CI, -8.5 to -4.3). In patients receiving mavacamten at week 32, and patients in the cross-over group after week 16, there were no clinically significant reductions in mean left ventricular ejection fraction, left ventricular stroke volume index, or left ventricular end-systolic and end-diastolic volumes. Neither group experienced any instances of death or ventricular tachyarrhythmia. Serious treatment-emergent adverse events were experienced at similar rates between both the mavacamten group at 32 weeks and cross-over group after week 16 (7.1% vs. 7.5%, respectively).
Chaitman et al.[24] (2004) CARISA Ranolazine ER 750 to 1,000 mg BID in combination with diltiazem, atenolol, or amlodipine vs placebo in combination with diltiazem, atenolol, or amlodipine	DB, MC, PC, PG, RCT Patients with symptomatic chronic angina despite treatment with diltiazem, atenolol, or amlodipine	N=823 12 weeks with long-term follow-up of up to 39 months	Primary: Exercise duration on treadmill Secondary: Time to inset of angina, time to ≥1 mm ST-segment depression, angina frequency, nitroglycerin use, survival	Primary: In the ranolazine group, exercise duration was significantly increased compared to placebo (P=0.01). Secondary: Time to angina and time to 1 mm ST-segment depression were significantly increased compared to placebo. Treatment with ranolazine significantly reduced the frequency of angina attacks (3.3 vs 2.5 attacks per week for the 750 mg group; P=0.006; and 3.3 vs 2.1 attacks per week for the 1,000 mg group; P<0.001), and nitroglycerin use compared to placebo. The most common adverse effects were constipation, dizziness, nausea, and asthenia (≤7.3% in the ranolazine group vs ≥0.7% in the placebo group). The survival rates for patients taking ranolazine were 98.4% (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				97.4 to 99.5) at year one and 95.9% (95% CI, 94.0 to 97.7) at year two.
Timmis et al.[25] (2006) CARISA Ranolazine ER 750 to 1,000 mg BID in combination with diltiazem, atenolol, or amlodipine vs placebo in combination with diltiazem, atenolol, or amlodipine	Post-hoc analysis of CARISA Patients with type 2 diabetes who had symptomatic chronic angina despite treatment with diltiazem, atenolol, or amlodipine	N=823 12 weeks with long-term follow-up of up to 39 months	Primary: Exercise duration on treadmill Secondary: Time to onset of angina, time to ≥1 mm ST-segment depression, angina frequency, nitroglycerin usage, and HbA_{1c} levels in diabetic patients only and lipid panel as post hoc analysis	Primary: In the CARISA trial, 23% of the patients were diabetic and 77% were not diabetic. The effects of ranolazine in the diabetic patients were comparable to those in the nondiabetic patients. There was no significant difference between the diabetic and nondiabetic patients in exercise duration (P=0.89), time to onset of angina (P=0.54), or time to ≥1 mm ST-segment depression (P=0.44). There was also no difference in the diabetic patients compared to the nondiabetic patients in angina frequency (P=0.81) or nitroglycerin consumption (P=0.063). Secondary: Compared to placebo, there were significant reductions in the HbA_{1c} levels in the ranolazine 750 mg (P=0.008) and ranolazine 1,000 mg (P=0.0002) treatment groups. A subgroup analysis showed that there were significant reductions in the HbA_{1c} levels in insulin-dependent diabetics treated with ranolazine (P=0.016 in the 750 mg group and P=0.008 in the 1,000 mg group). The non-insulin-dependent patients in the ranolazine-treated group showed a significant reduction in HbA_{1c} with the 1,000 mg dose (P=0.007), but not with the 750 mg dose (P=0.087). Treatment with ranolazine 750 mg was associated with an increase in low-density lipoprotein and total cholesterol, while treatment with ranolazine 1,000 mg did not have any effects on the lipids profile.
Stone et al.[26] (2006) ERICA Ranolazine ER 1,000 mg BID in combination with amlodipine vs	DB, PC, PG, RCT Stable patients with coronary disease and ≥3 anginal attacks per week despite maximum recommended dosage of amlodipine	N=565 6 weeks	Primary: Frequency of angina episodes per week Secondary: Average weekly nitroglycerin consumption rate, SAQ, safety as assessed by	Primary: Angina frequency at baseline averaged 5.63 episodes per week. Treatment with ranolazine significantly reduced the frequency of angina episodes per week compared to placebo (2.88 vs 3.31; P=0.028). Secondary: Nitroglycerin consumption use at baseline averaged 4.72 tablets per week. Ranolazine treatment significantly reduced the use of nitroglycerin compared to placebo (2.03 vs 2.68; P=0.014). The SAQ scores on angina frequency were significantly improved in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo in combination with amlodipine			adverse events and electrocardiogram	ranolazine arm compared to placebo arm (P=0.008). There were no significant differences between treatment groups in the other SAQ measures, such as physical limitation, anginal stability, disease perception, and treatment satisfaction.
Chaitman et al.[27] (2004) MARISA Ranolazine ER 500 to 1,500 mg BID vs placebo Patients discontinued anti-anginal medications prior to randomization.	DB, PC, RCT, XO Patients with coronary artery disease and ≥3 month history of effort angina that had previously responded to antianginal agents	N=191 4 weeks with long-term follow-up of up to 36 months	Primary: Exercise duration Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak, exercise duration at peak, long-term survival	Primary: Treatment with ranolazine at all doses resulted in significant increases in exercise duration (P<0.001). Secondary: Treatment with ranolazine at all doses resulted in significant increases in time to angina (P<0.001) and time to 1 mm ST-segment depression (P<0.001). No clinically significant changes in heart rate or BP at rest or exercise were observed. The rates of adverse events were similar for the 500 mg and placebo group, but higher with the 1,000 and 1,500 mg groups (15.6% for placebo, 16.0% for 500 mg, 21.7% for 1,000 mg, and 34.2% for 1,500 mg). The survival rates were 96.3% (95% CI, 93.0 to 99.5) at one year and 93.6% (95% CI, 89.3 to 98.0) at two years.
Koren et al.[28] (2007) Ranolazine ER 500 to 1,000 mg BID	MC, OL Patients with chronic angina who had completed the MARISA or CARISA trial	N=746 2.82 years (mean duration)	Primary: Discontinuation, adverse events, electrocardiogram findings, and mortality	Primary: 571 patients (76.7%) remained on therapy while 72 patients (9.7%) discontinued due to adverse events two years after initial dosing. There was a significant correlation between patient age >64 years and increased rates of discontinuation related to adverse events (RR, 2.32; P<0.001). A significantly lower correlation of adverse event-related discontinuation was seen in patients with a history of congestive heart failure (RR, 0.55; P=0.030). Compared to baseline, a mean prolongation of approximately 2.4 microseconds in the QT interval was observed (P<0.001). However there were no significant differences in PR or QRS intervals during this time. A total of 64 deaths (all causes) occurred during the 2,102 patient-years

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(3.0% annual incidence) of the study. This translates to a 97.2% and 94.4%, one- and two-year survival from this incidence.
Rich et al.[29] (2007) Ranolazine ER 750 to 1,000 mg BID vs placebo	MA Patients ≥70 years of age with symptomatic chronic angina despite treatment diltiazem, atenolol, or amlodipine	N=1,387 (2 trials) 6 weeks	Primary: Improvement in younger patients (<70 years of age) and older patients (≥70 years of age) in exercise times, angina frequency, and adverse events Secondary: Not reported	Primary: Overall ranolazine significantly improved exercise duration and time to onset of angina during exercise testing (P≤0.03). There was no difference on exercise time in younger patients compared to older patients (P>0.8). Older patients tended to have fewer angina episodes (a mean of 3.21 in the placebo group and 2.08 in the ranolazine 1,000 mg group) than younger patients (a mean of 4.16 in the placebo group and 3.11 in the ranolazine 1,000 mg group). Adverse events were more commonly reported in the older patient population (32.6% in the placebo group and 44.2% in the ranolazine group) compared to the younger patients (31.2% in the placebo group and 32.1% in the ranolazine group). Secondary: Not reported
Kosiborod et al.[30] (2013) TERISA Ranolazine (target dose 1000 mg BID) vs placebo (all patients underwent 4 week placebo run-in period)	DB, MC, PC, RCT Patients with diabetes, CAD, and stable angina treated with 1 to 2 antianginals	N=927 8 weeks	Primary: Average weekly number of anginal episodes over the last 6 weeks of the study Secondary: Average weekly frequency of SL NTG use, number of angina-free days, proportion of subjects with ≥50% reduction in average weekly	Primary: Though patients treated with placebo had a substantial decrease in angina frequency, weekly angina frequency was significantly lower in the ranolazine group than in the placebo group during weeks two to eight after randomization (3.8 vs 4.3 episodes; P=0.008). Secondary: At baseline, there was no statistical difference in average weekly SL NTG use between the ranolazine and placebo groups (4.1 vs 4.5 doses; P=0.27). During weeks two to eight after randomization, the average weekly number of SL NTG doses was significantly lower in the ranolazine group, and was significantly lower in the ranolazine group than in the placebo group (1.7 vs 2.1 doses; P=0.003). The proportion of angina-free days did not differ between the ranolazine and placebo groups (67 vs 64%; P=0.068). The proportion of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			angina frequency, and health-related quality of life, as assessed by SF-36	achieving at least 50% reduction in weekly angina frequency was higher in the ranolazine than placebo group (47 vs 42%; P=0.034), and the increase from baseline to end of treatment in SF-36 Physical Component Summary Score was also greater in the ranolazine than placebo group (2.9 [95% CI, 2.3 to 3.5] points vs 1.9 [95% CI, 1.3 to 2.5] points; P=0.005). However, these latter two differences were not considered statistically significant (despite P-values <0.05) based on the pre-specified multiple testing procedure.
Weisz et al.[31] (2016) RIVER-PCI Ranolazine 1000 mg BID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a history of chronic angina with incomplete revascularization after PCI (defined as one or more lesions with ≥50% diameter stenosis in a coronary artery ≥2 mm diameter)	N=2,604 median follow-up of 643 days	Primary: Time to first occurrence of ischemia-driven revascularization or ischaemia-driven hospitalization without revascularization Secondary: Time from randomization to the first occurrence of sudden cardiac death, cardiovascular death, or MI	Primary: The composite primary endpoint occurred in 345 (26%) patients assigned to ranolazine and 364 (28%) patients assigned to placebo (HR, 0.95; 95% CI, 0.82 to 1.10; P=0.48). Secondary: The key secondary efficacy endpoints of sudden cardiac death, cardiovascular death, and MI occurred with similar frequency in both groups. The incidence of major adverse cardiovascular events, all-cause mortality, stroke, or hospitalization for heart failure likewise did not differ significantly between groups; however, the incidence of adjudicated transient ischemic attack events was higher in patients given ranolazine. 189 (14%) patients in the ranolazine group and 137 (11%) patients in the placebo group discontinued study drug because of an adverse event (P=0.04).
Cocco et al.[32] (1992) Ranolazine IR* 10, 60, 120, or 240 mg single dose in addition to beta-blocker or diltiazem	DB, MC, PC, RCT, XO Patients with chronic stable angina who remained symptomatic despite treatment with beta-blockers or	N=104 4 to 9 days	Primary: Exercise duration, time to angina, time to ≥1 mm ST-segment depression Secondary: Heart rate, BP	Primary: Exercise duration, time to angina, and time to 1 mm ST-segment depression were significantly improved with ranolazine 240 mg dose only in the beta-blocker group and the groups combined (P<0.05 for both). There was no significant difference in exercise duration, time to angina, or time to 1 mm ST-segment depression with ranolazine treatment in patients that were on the diltiazem regimen (P>0.05 for all). Secondary: Treatment with ranolazine did not result in significant changes in heart

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo in addition to beta-blocker or diltiazem	diltiazem			rate or BP compared to placebo (P>0.05).
Pepine et al.[33] (1999) Ranolazine IR* 400 mg BID, 267 mg TID, or 400 mg TID vs placebo	DB, MC, PC, RCT, XO Patients with chronic stable angina that responded to conventional antianginal therapy	N=312 5 weeks	Primary: Time to angina onset, exercise duration, and time to 1 mm ST-segment depression at peak and trough concentrations Secondary: Safety	Primary: At peak ranolazine concentrations, time to angina onset (P≤0.02), exercise duration (P=0.013), and time to 1 mm ST-segment depression were significantly improved with all dosing regimens. At trough ranolazine concentrations, only time to 1 mm ST-segment depression was significantly improved (P=0.047). Secondary: The rates of adverse effects were similar in the ranolazine groups and placebo group. Only minor gastrointestinal adverse effects were reported more frequently with ranolazine than placebo (6.6 to 10.7 vs 3.2%).
Rousseau et al.[34] (2005) Ranolazine IR* 400 mg TID for 7 to 10 days vs atenolol 100 mg QD for 7 to 10 days vs placebo for 7 to 10 days	DB, MC, PC, XO Patients with coronary artery disease and chronic angina who were on standard doses of atenolol	N=158 7 to 10 days	Primary: Time to onset of angina Secondary: Time to 1 mm ST-segment depression, total exercise duration, angina frequency, nitroglycerin use	Primary: Treatment with ranolazine and atenolol both resulted in significant increases in time to angina, exercise duration, and time to 1 mm ST-segment depression when compared to placebo (P<0.05 for all). Secondary: There was no significant difference between ranolazine and atenolol in the time to angina (P=0.18), time to 1 mm ST-segment depression (P=0.86), angina frequency, or nitroglycerin use. However, the increase in exercise duration was significantly greater in the ranolazine group than atenolol (mean difference of 21.1 seconds, 95% CI, 6.2 to 36.0; P=0.006).
Morrow et al.[35] (2007) MERLIN-TIMI 36	DB, MC, PC, RCT Patients ≥18 years	N=6,560 1 year	Primary: Composite of cardiovascular	Primary: The composite of cardiovascular death, MI or recurrent ischemia occurred in 21.8% of the patients in the ranolazine group and 23.5% of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine ER 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-STEMI ≥3)		death, MI, or recurrent ischemia Secondary: Composite of cardiovascular death, MI, or severe recurrent ischemia, rate of failure of therapy (cardiovascular death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new or worsening heart failure, or an early positive ETT), safety	the placebo group (HR, 0.92; 95% CI, 0.83 to 1.02; P=0.11). Secondary: The composite of cardiovascular death, MI, or severe recurrent ischemia occurred in 18.7% of patients in the ranolazine group compared to 19.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.86 to 1.08; P=0.50). Failure of therapy occurred in 36.8% of patients in the ranolazine group and 38.3% of patients in the placebo group (HR, 0.94; 95% CI, 0.87 to 1.02; P=0.16). Cardiovascular death occurred in 4.4% of patients in the ranolazine group and 4.5% of patients in the placebo group (HR, 1.00; 95% CI, 0.79 to 1.25; P=0.98). MI occurred in 7.4% of patients in the ranolazine group and 7.6% of patients in the placebo group (HR, 0.97; 95% CI, 0.81 to 1.16; P=0.76). Recurrent ischemia occurred in 13.9% of patients in the ranolazine group and 16.1% of patients in the placebo group (HR, 0.97; 95% CI, 0.76 to 0.99; P=0.03). There was no difference in the documented symptomatic arrhythmias in the ranolazine group (3.0%) and the placebo group (3.1%; P=0.84).
Scirica et al.[36] (2007) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine ER 1,000 mg orally BID vs	DB, MC, PC, RCT Patients ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of	N=6,560 7 days	Primary: Incidence of clinically significant arrhythmias Secondary: Not reported	Primary: Ventricular tachycardia ≥3 beats ≥100 bpm was significantly less in the ranolazine group (52.1%) compared to placebo (60.6%) (RR, 0.86; 95% CI, 0.82 to 0.90; P<0.001). Ventricular tachycardia ≥4 beats ≥100 bpm was significantly less in the ranolazine group (20.9%) compared to placebo (29.5%) (RR, 0.71; 95% CI, 0.6 to 0.78; P<0.001). Ventricular tachycardia ≥8 beats (lasting <30 seconds) was significantly less in the ranolazine group (5.3%) compared to placebo (8.3%) (RR, 0.63; 95% CI, 0.52 to 0.76; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Study medication was administered in addition to standard therapy.	necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-STEMI ≥3)			There was no significant difference in polymorphic ventricular tachycardia ≥8 beats in the ranolazine group (1.2%) compared to placebo (1.4%) (RR, 0.83; 95% CI, 0.54 to 1.28; P=0.40). There was no significant difference in sustained ventricular tachycardia (≥30 seconds) in the ranolazine group (0.44%) compared to placebo (0.44%) (RR, 1.01; 95% CI, 0.48 to 2.13; P=0.98). This includes monomorphic (0.13 vs 0.22%; RR, 0.59; 95% CI, 0.17 to 2.06; P=0.37) and polymorphic (0.32 vs 0.22%; RR, 1.41; 95% CI, 0.52 to 3.78; P=0.46). There was no significant difference in new-onset AF in the ranolazine group (1.7%) compared to placebo (2.4%) (RR, 0.74; 95% CI, 0.52 to 1.05; P=0.08). Other supraventricular arrhythmias ≥120 bpm lasting at least 4 beats were significantly less in the ranolazine group (44.7%) compared to placebo (55.0%) (RR, 0.81; 95% CI, 0.77 to 0.85; P<0.001). Secondary: Not reported
Wilson et al.[37] (2009) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine ER 1,000 mg orally BID vs placebo	Subgroup analysis of MERLIN-TIMI 36 of patients with a history of prior chronic angina Patients ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated	N=3,565 1 year	Primary: Time to first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia Secondary: Anginal episodes, need for an increase or addition of any antianginal therapy, and	Primary: The time to the first occurrence of the composite of cardiovascular death, MI, or recurrent ischemia was lower in patients treated with ranolazine compared to placebo among patients with prior angina (25.2 vs 29.4%, respectively, HR, 0.86; 95% CI, 0.75 to 0.97; P=0.017). This effect was due to the effects of ranolazine on recurrent ischemia. Ranolazine had no effect on the risk of cardiovascular death or MI among patients with prior angina (HR, 0.97; 95% CI, 0.80 to 1.16; P=0.71). Secondary: Ranolazine reduced the incidence of recurrent ischemia (HR, 0.78; 95% CI, 0.67 to 0.91; P=0.002), worsening angina (HR, 0.77; 95% CI, 0.59 to 1.00; P=0.048), and intensification of antianginal therapy (HR, 0.77; 95% CI, 0.64 to 0.92, P=0.005) compared to placebo among patients with prior angina.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study medication was administered in addition to standard therapy.	biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-STEMI ≥3)		exercise duration on treadmill or bicycle ETT performed at 8 months, safety, incidence of clinically significant arrhythmias	Ranolazine improved severe recurrent ischemia compared to placebo among patients with prior angina (11.9 vs 14.4%, respectively; HR, 0.81; 95% CI, 0.67 to 0.98; P=0.026). The mean number of traditional antianginal agents was decreased with ranolazine compared to placebo among patients with prior angina (2.8 vs 2.9, respectively; P=0.045). Ranolazine significantly improved all metrics of exercise performance on ETT or bicycle exercise testing compared to placebo among patients with prior angina. Ranolazine was generally well tolerated in patients with prior angina. The most common adverse effects with ranolazine compared to placebo were dizziness (12.4 vs 7.4%, respectively), nausea (9.7 vs 6.1%, respectively), and constipation (8.5 vs 3.3%, respectively). No significant increase in frequency of symptomatic documented arrhythmias was observed with ranolazine compared to placebo among patients with prior angina (risk ratio, 0.98; 95% CI, 0.67 to 1.43; P=0.92). Clinically significant arrhythmias were significantly lower in the ranolazine group (73.9 vs 83.1%, respectively; P=0.0001).
Mega et al.[38] (2010) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine ER 1,000 mg orally BID vs placebo	Subgroup analysis of MERLIN-TIMI 36 of women Women ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of	N=2,291 1 year	Primary: Time to first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia in women Secondary: Anginal episodes, incidence of clinically significant	Primary: Treatment with ranolazine was associated with a 29% reduction in recurrent ischemia in women compared to placebo (13.0 vs 18.2%; HR, 0.71; 95% CI, 0.57 to 0.88; P=0.002). There was no significant reduction in cardiovascular death or MI with ranolazine compared to placebo in women (P=0.80). Secondary: Treatment with ranolazine was associated with less angina compared to placebo in women (P<0.001). Fewer women treated with ranolazine needed to undergo intensification of their antianginal medical regimen compared to placebo (10.4 vs 14.4%, respectively; P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study medication was administered in addition to standard therapy.	necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-STEMI ≥3)		arrhythmias	There was no difference in symptomatic documented arrhythmias in women treated with ranolazine vs placebo (2.6 vs 2.6%, respectively; P=0.95). Treatment with ranolazine was associated with fewer episodes of ventricular arrhythmias compared to placebo (P=0.008).
Metha et al.[39] (2011) Ranolazine for 4 weeks vs placebo for 4 weeks	DB, PC, XO (pilot trial) Women with angina, evidence of myocardial ischemia (signs and symptoms), but no obstructive coronary artery disease	N=20 10 weeks	Primary: Seattle Angina Questionnaire, cardiac magnetic resonance Secondary: Not reported	Primary: Patients receiving ranolazine had significantly higher (better) Seattle Angina Questionnaire scores, including physical functioning (P=0.046), angina stability (P=0.008), and QOL (P=0.021). There was a trend toward a higher (better) cardiac magnetic resonance mid-ventricular myocardial perfusion reserve index (2.4 vs 2.1; P=0.074) with ranolazine. Secondary: Not reported
Maurer et al.[40] (2018) ATTR-ACT Tafamidis 80 mg daily vs tafamidis 20 mg daily vs placebo	DB, MC, RCT Patients 18 to 90 years of age, transthyretin amyloid cardiomyopathy (hATTR or ATTRwt) confirmed by biopsy from cardiac and noncardiac sites or presence of transthyretin precursor protein, cardiac involvement	N=441 30 months	Primary: All-cause mortality and frequency of cardiovascular-related hospitalizations Secondary: Change from baseline in the 6MWT and KCCQ-OS	Primary: All-cause mortality and rates of cardiovascular-related hospitalizations were lower among the 264 patients who received tafamidis than among the 177 patients who received placebo (P<0.001). Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] vs 76 of 177 [42.9%]; HR, 0.70; 95% CI, 0.51 to 0.96) and a lower rate of cardiovascular-related hospitalizations, with a relative risk ratio of 0.68 (0.48 per year vs 0.70 per year; 95% CI, 0.56 to 0.81). Secondary: At month 30, tafamidis was also associated with a lower rate of decline in distance for the 6-minute walk test at 75.68 m (P<0.001) and a lower rate of decline at 13.65 in KCCQ-OS score (P<0.001) as compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	confirmed by echocardiography, history of heart failure with one prior hospitalization for heart failure, NT-proBNP level ≥600 pg/mL, and a 6MWT > 100 m, without NYHA class IV heart failure, history of liver or heart failure, or previous treatment with tafamidis			

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended release, IR=immediate-release, IV=intravenous, 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, SR=sustained-release, XO=cross-over
Miscellaneous abbreviations: 6MWT= six-minute walk test, AF=atrial fibrillation, ATTRwt=wild type transthyretin amyloidosis, BP=blood pressure, CI=confidence interval, ETT=exercise tolerance test, hATTR=hereditary transthyretin amyloidosis, HbA_{1c}=glycosylated hemoglobin, HCMSQ-SoB= Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore, HR=hazard ratio, KCCQ-23-CSS= Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score, KCCQ-CCS= Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score, KCCQ-OS=Kansas City Cardiomyopathy Questionnaire–Overall Summary, LVOT=left ventricular outflow tract, MI=myocardial infarction, NT-proBNP=N-terminal pro-B-type natriuretic peptide, NYHA=New York Heart Association, PCI= percutaneous coronary intervention, QOL=quality of life, RR=relative risk, SAQ=Seattle Angina Questionnaire, SRT=septal reduction therapy, STEMI=ST-elevation myocardial infarction, TIMI=thrombolysis in myocardial infarction

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
Ling et al retrospectively reviewed the medical records of 150 consecutive patients with refractory angina treated with ranolazine. During the 12 months prior to and during the 12 months of treatment with ranolazine there were fewer clinic visits and emergency department visits during ranolazine treatment than in the pre-ranolazine period, but the difference in frequency of these visits was not statistically significant. The number of hospitalizations was significantly reduced during treatment with ranolazine compared with the pre-ranolazine treatment period (P=0.002).[41]

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 Cardiac Drugs, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ivabradine	tablet, solution	Corlanor®	$$$$$	N/A
Mavacamten	capsule	Camzyos®	$$$$$	N/A
Ranolazine	extended-release tablet, extended-release granules	Aspruzyo Sprinkle® ER, Ranexa®*	$$$$$	$
Tafamidis	capsule	Vyndamax®, Vyndaqel®	$$$$$	N/A

N/A=Not available.

X. Conclusions

Ranolazine is approved for the treatment of chronic angina. It may be used in combination with β-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid lowering therapy, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers. The exact mechanism of ranolazine is unknown. The anti-ischemic and antianginal effects do not depend upon reductions in heart rate or blood pressure.[2] Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection

fraction ≤35%, who are in sinus rhythm with resting heart rate ≥70 beats per minute and either are on maximally tolerated doses of β-blockers or have a contraindication to β-blocker use. It has also been approved for the treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients aged six months and older, who are in sinus rhythm with an elevated heart rate. Ivabradine reduces sinus rate by blocking the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker I_f current, which regulates heart rate.[3,4] Tafamidis is a transthyretin (TTR) stabilizer indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.[5] Tafamidis binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.[5] Ranolazine is available in a generic formulation.

There are several organizations that provide recommendations on the treatment of chronic angina. β-blockers are considered first-line therapy for reducing symptoms of angina in patients with coronary artery disease. Long-acting calcium channel blockers or long-acting nitrates may be used in combination with β-blockers if initial therapy is not successful, or if β-blockers are contraindicated. Available guidelines recommend ranolazine as an alternative agent when β-blockers, calcium channel blockers, and nitrates are not adequately effective or are not tolerated.[8,9] The American College of Cardiology/American Heart Association Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes states that ranolazine may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia.[9]

In clinical trials, ranolazine (administered either as monotherapy or in combination with other anti-anginal drugs) was more effective compared to placebo with regards to exercise duration, time to onset of angina, frequency of angina, and nitroglycerin use.[24,26,27,30] In the MERLIN-TIMI 36 trial, there was no beneficial effect on cardiovascular outcomes with ranolazine compared to placebo in patients with acute coronary syndrome.[2,35] Ventricular arrhythmias were less common with ranolazine; however, this did not lead to a reduction in mortality, arrhythmia hospitalization or arrhythmia symptoms.[2,35,36] Tolerance to ranolazine did not develop after 12 weeks of therapy. Rebound increases in angina, as measured by exercise duration, have not been observed following abrupt discontinuation of ranolazine.[2]

Corlanor® (ivabradine) is indicated to reduce the risk of hospitalization for worsening HF in a small subset of HF patients.[3,4] In general guidelines recommend considering the use of ivabradine in line with the FDA-approved indications.[13-14] The approval of ivabradine was based mainly on global clinical data from a phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial named SHIFT (Systolic Heart Failure treatment with the I_f inhibitor ivabradine Trial). This trial compared the use of ivabradine to placebo in addition to standard of care (SOC) therapies in 6,558 clinically stable patients in sinus rhythm with reduced LVEF ≤ 35%, heart rate (HR) ≥70 bpm, and with a hospitalization for HF within the past 12 months. The SOC generally included a β-blocker (89%), ACEI and/or ARB (91%), diuretics (83%) and an aldosterone antagonist (60%).[19] Results showed that ivabradine significantly reduced the risk of hospitalization or cardiovascular death for worsening HF, with 672 (21%) of patients on placebo compared to 514 (16%) of those on ivabradine experiencing a hospital admission (hazard ratio, 0.74; 95% confidence interval, 0.66 to 0.83; P<0.0001). Guideline recommendations are consistent with the FDA-approved indications for ivabradine.[14]

Tafamidis (Vyndaqel® and Vyndamax®) is the first FDA-approved treatment for cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults.[5] In clinical studies, treatment with tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life.[5,40] Clinical guidelines reference the studies and data supporting the use of tafamidis.[16]

Mavacamten (Camzyos®) is indicated for the treatment of adults with symptomatic New York heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.[8] In clinical studies, treatment with mavacamten was associated with improvements in peak oxygen consumption, NYHA functional class, and various cardiomyopathy questionnaires including the Kansas City Cardiomyopathy Questionnaire and Hypertrophic Cardiomyopathy Symptom Questionnaire as compared with placebo.[22,23] Mavacamten is available only through a Risk Evaluation and Mitigation Strategy (REMS) program due to the risk of reduced left ventricular ejection fraction and heart failure.[8] Clinical guidelines do not currently include mavacamten regarding recommendations for managing patients with obstructive hypertrophic cardiomyopathy.

There is insufficient evidence to support that one brand miscellaneous cardiac drug is safer or more efficacious than other agents commonly used for the approved indication. Due to their limited FDA-approved indications, ivabradine, mavacamten, and tafamidis should be available through the medical justification portion of the prior authorization process for their respective indications.

Therefore, all brand miscellaneous cardiac drugs 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 miscellaneous cardiac drug 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Bile Acid Sequestrants
AHFS Class 240604
February 7, 2024

I. Overview

Dyslipidemia is a complex of related conditions that affects many individuals. Low-density lipoprotein cholesterol (LDL-C) is considered the primary target of cholesterol lowering therapy. Many studies have demonstrated that elevated concentrations of LDL-C are a major risk factor for coronary heart disease, and lowering LDL-C will reduce the risk for major coronary events. Non-high-density lipoprotein cholesterol is a secondary target of therapy in patients with elevated triglycerides (≥200 mg/dL). This parameter takes into account the atherogenic potential associated with remnant lipoproteins in patients with hypertriglyceridemia. High-density lipoprotein cholesterol (HDL-C) has been shown to be an independent predictor of cardiovascular mortality and is considered an LDL modifying risk factor; however, there is insufficient data to warrant setting a specific goal for raising HDL-C. The independent effect of raising HDL-C or lowering triglycerides on the risk of cardiovascular morbidity and mortality has not been determined.[1]

The antilipemic agents are categorized into six different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins), proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Bile acids are secreted into the intestines during digestion to emulsify fat and lipids to facilitate their absorption. Most of the bile acids are reabsorbed and returned to the liver via enterohepatic circulation. The bile acid sequestrants bind to bile acids and form a complex, which is then excreted in the feces. The reduction in bile acids increases the oxidation of cholesterol to bile acids.[2-4] There is a subsequent increase in the number of LDL receptors in the liver, which increases hepatic uptake of LDL-C and reduces serum cholesterol levels. Bile acid sequestrants can decrease LDL-C by 15 to 30% and increase HDL-C by 3 to 5%. Triglycerides may increase or remain unchanged.[1]

The bile acid sequestrants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in a generic formulation. This class was last reviewed in February 2022.

Table 1. Bile Acid Sequestrants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cholestyramine	packet for oral suspension, powder for oral suspension	Questran®*†, Questran Light®*‡	cholestyramine, cholestyramine light
Colesevelam	packet for oral suspension, tablet	Welchol®*	colesevelam
Colestipol	granules for oral suspension, packet for oral suspension, tablet	Colestid®*	colestipol

*Generic is available in at least one dosage form or strength.
†Contains sucrose.
‡Contains aspartame.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the bile acid sequestrants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Bile Acid Sequestrants

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[5]	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)[1]**	General recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant, or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy, and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout, and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. Omega-3 fatty acids • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses.

Clinical Guideline	Recommendation
	• In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2017)[6] and Executive Summary (2020)[7]**	<u>Cholesterol Goals</u> • For patients at low risk for ASCVD (i.e., no risk factors), goals of LDL-C<130 mg/dL, non-HDL-C<160 mg/dL, and TG<150 mg/dL are recommended. • For patients at moderate risk for ASCVD (i.e., two or fewer risk factors and a calculated 10-year risk of <10%), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at high risk for ASCVD (i.e., two or more risk factors and a 10-year risk between 10% and 20% or who have diabetes or stage ≥3 CKD with no other risk factors), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at very high risk for ASCVD (i.e., established clinical ASCVD or recent hospitalization for ACS, carotid or peripheral vascular disease, or 10-year risk >20%; diabetes with one or more risk factor(s); CKD stage 3 or higher with albuminuria; or HeFH), goals of LDL-C<70 mg/dL, non-HDL-C<100 mg/dL, apo B<80 mg/dL, and TG<150 mg/dL are recommended. • For individuals at extreme risk (i.e., progressive ASCVD including unstable angina that persists after achieving an LDL-C <70 mg/dL; established clinical ASCVD in individuals with diabetes, CKD stage 3 or higher, and/or HeFH); history of premature ASCVD (<55 years of age for males or <65 years of age for females), goals of LDL-C<55 mg/dL, non-HDL-C<80 mg/dL, apo B<70 mg/dL, and TG<150 mg/dL are recommended. • An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100 to 129 mg/dL considered "borderline" and 130 mg/dL or greater considered "high" (based on recommendations from the American Academy of Pediatrics). • Due to its potential cardioprotective role, HDL-C should be >40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C. <u>General Recommendations</u> • A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes and patient education with pharmacotherapy as needed to achieve evidence based targets. • A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include ≥30 minutes of moderate-intensity physical activity [consuming 4 to 7 kcal/min] four to six times weekly, with an expenditure of ≥200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting

Clinical Guideline	Recommendation
	activities. • Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs. • In addition to aerobic activity, muscle-strengthening activity is recommended at least two days a week. • For adults, a reduced-calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains (primarily whole grains), fish, and lean meats is recommended. • For adults, the intake of saturated fats, trans-fats, and cholesterol should be limited, while LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10 to 25 g/day). • Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children. • Excessive alcohol intake should be avoided. • Tobacco cessation should be strongly encouraged and facilitated. • In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals. <u>Statins</u> • Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. • For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction. • In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered. • Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, who also have at least one additional risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL. • Extreme risk individuals should be treated with statins to target an even lower LDL-C treatment goal of <55 mg/dL. <u>Fibrates</u> • Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). • Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add fibrate. • In patients treated with a statin and icosapent ethyl with TG≥150 mg/dL, a fibrate may be considered. <u>Omega-3 Fish Oil</u> • Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose. • Omega-3 should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should

Clinical Guideline	Recommendation
	be given to add omega-3. <u>Niacin</u> • Niacin therapy is recommended principally as an adjunct for reducing TG. • Niacin therapy should not be used in individuals aggressively treated with statin due to absence of additional benefits with well-controlled LDL-C. • Niacin should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add niacin. • In patients treated with a statin and icosapent ethyl with TG>150 mg/dL, niacin may be considered. <u>Icosapent Ethyl</u> • Icosapent ethyl (two grams twice daily) should be added to a statin in any patient with established ASCVD or diabetes with two or more ASCVD risk factors and triglycerides between 135 to 499 mg/dL to prevent ASCVD events. <u>Bile Acid Sequestrants</u> • Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG. <u>Cholesterol Absorption Inhibitors</u> • Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals. • Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk. <u>PCSK9 Inhibitors</u> • Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH. • PCSK9 inhibitors should be considered in patients with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals. <u>Combination Therapy</u> • Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal. <u>Special Considerations: Women</u> • Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient. • Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended. <u>Special Considerations: Children and Adolescents</u> • Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, and particularly for those satisfying the following criteria: o LDL-C ≥190 mg/dL o LDL-C ≥160 mg/dL and the presence of two or more cardiovascular risk

Clinical Guideline	Recommendation
	factors, even after vigorous intervention o Family history of premature ASCVD (before 55 years of age), or o Having overweight, obesity, or other elements of the insulin resistance syndrome <u>Follow-up and Monitoring</u> • Reassess individuals' lipid status six weeks after therapy initiation and again at six-week intervals until the treatment goal is achieved. • While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals. • While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment. • More frequent lipid status evaluation is recommended in situations such as deterioration of diabetes control, use of a new drug known to affect lipid levels, progression of atherothrombotic disease, considerable weight gain, unexpected adverse change in any lipid parameter, development of a new ASCVD risk factor, or convincing new clinical trial evidence or guidelines that suggest stricter lipid goals. • Liver transaminase levels should be measured before and three months after niacin or fibric acid treatment initiation because most liver abnormalities occur within 3 months of treatment initiation. Liver transaminase levels should be measured periodically thereafter (e.g., semiannually or annually). • Creatine kinase levels should be assessed and the statin discontinued, at least temporarily, when an individual reports clinically significant myalgias or muscle weakness on statin therapy.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (2018)**[8]	<u>Top 10 messages to reduce risk of atherosclerotic cardiovascular disease through cholesterol management</u> • In all individuals, emphasize a heart-healthy lifestyle across the life course. • In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. o Clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin. • In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy. Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. • In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. • In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. • In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin

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	therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 to 189 mg/dL (≥1.8 to 4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium (CAC). • Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement four to 12 weeks after statin initiation or dose adjustment, repeated every three to 12 months as needed. <u>Recommendations for Statin Therapy Use in Patients With ASCVD</u> • In patients who are 75 years of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. • In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels. • In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe. • In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost. • In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy. • In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences. • In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. • In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe. • In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (three to five years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events. <u>Recommendations for primary severe hypercholesterolemia (LDL-C ≥190 mg/dL)</u> • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher, maximally tolerated statin therapy is recommended. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher, ezetimibe therapy is reasonable. • In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL, who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL, while taking maximally tolerated statin and ezetimibe therapy, the

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	addition of a bile acid sequestrant may be considered. • In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. • In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher and who achieve an on-treatment LDL-C level of 130 mg/dL or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. <u>Recommendations for patients with diabetes mellitus</u> • In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. <u>Primary prevention recommendations for adults 40 to 75 years of age with LDL levels 70 to 189 mg/dL</u> • In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more. • For the primary prevention of clinical ASCVD in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL, the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%). • Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision. • In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy. • In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND o If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); o If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥ 55 years of age; o If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy • In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin. • In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Recommendations for older adults</u> • In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL,

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	initiating a moderate-intensity statin may be reasonable. • In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy. • In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL, it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy. <u>Recommendations for children and adolescents</u> • In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity. • In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C. • In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL or higher with a clinical presentation consistent with familial hypercholesterolemia (FH) and who do not respond adequately with three to six months of lifestyle therapy, it is reasonable to initiate statin therapy. • In children and adolescents with a family history of either early CVD or significant hypercholesterolemia, it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age two years to detect FH or rare forms of hypercholesterolemia. • In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia. • In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome. • In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of nine and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities. <u>Recommendations for hypertriglyceridemia</u> • In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides. • In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy. • In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy. • In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL, and especially fasting triglycerides ≥1000 mg/dL), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a

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	very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy. <u>Recommendations for statin safety and statin-associated side effects</u> • A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully. • In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors. • In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and SAMS, is recommended before initiation of treatment. • In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy. • In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss. • In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity. • In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks. • In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit. • Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS. • In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)[9]**	<u>Statin treatment</u> • The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-

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	drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. • For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%. • Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. • Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. • Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders.

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	○ Unexplained alanine transaminase elevations >3 times upper limit of normal. ○ Patient characteristics or concomitant use of drugs affecting statin metabolism. ○ >75 years of age. • Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: ○ History of hemorrhagic stroke. ○ Asian ancestry. • Creatine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). • Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug). • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: ○ To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. ○ If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: ○ Discontinue the statin until the symptoms can be evaluated. ○ Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica,

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	steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. • In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have

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	been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. <u>Non statin safety</u> • Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. • Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. • In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. • To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. • Bile acid sequestrants should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. • A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. • It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. • It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. • Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. • Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. • Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day.

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	• If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)[10]**	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control

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	and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD.

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	• In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. Recommendations for treatment of tobacco use • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. Recommendations for aspirin use • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2021)**[11]	Drugs • Currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins), fibrates, bile acid sequestrants, selective cholesterol absorption inhibitors (e.g., ezetimibe) and, more recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and bempedoic acid. Response to all therapy varies widely among individuals and therefore monitoring the effect on LDL-C levels is recommended. • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins also lower triglycerides, and may reduce pancreatitis risk. • Statins should be used as the drugs of first choice in patients at increased risk of ASCVD. • Selective cholesterol absorption inhibitors (ezetimibe) should be considered as second-line therapy, either on top of statins when the therapeutic goal is not achieved, or when a statin cannot be prescribed. • Among patients in whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C levels when administered in combination with ezetimibe. • PCSK9 inhibitors also lower triglycerides, raise HDL-C and apolipoprotein A-I,

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	and lower lipoprotein(a), although the relative contributions of these lipid modifications remain unknown. • PCSK9 inhibitors decrease LDL-C by up to 60%, either as monotherapy or in addition to the maximal statin dose or other lipid-lowering therapies (ezetimibe). • Fibrates are used primarily for triglyceride lowering and, occasionally, for increasing HDL-C. Evidence supporting the use of these drugs for CVD event reduction is limited and, given the strong evidence favoring statins, routine use of these drugs in CVD prevention is not recommended. In order to prevent pancreatitis, when triglycerides are >10 mmol/L (>900 mg/dL) they must be reduced not only by drugs but also by restriction of alcohol, treatment of DM, withdrawal of estrogen therapy, etc. In those rare patients with severe primary hypertriglyceridemia, specialist referral must be considered. <u>Recommendations for pharmacological low-density lipoprotein cholesterol lowering for those <70 years of age</u> • It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group. • If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. • For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered. • For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may be considered. • If the goal is not achieved, statin combination with a bile acid sequestrant may be considered.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2021)**[12]	<u>Secondary Stroke Prevention</u> • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or transient ischemic attack (TIA) presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other clinical ASCVD. • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, and LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD. • Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2018 ACC/AHA cholesterol guidelines, which include lifestyle modifications, dietary recommendations, and medication recommendations. <u>Treatment of Hypertriglyceridemia</u> • In patients with ischemic stroke or TIA with fasting TG 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL, on moderate or high-intensity statin, with HbA_{1c} <10%, and with no history of pancreatitis, AF, or severe heart failure, treatment with icosapent ethyl (IPE) 2 g twice a day is reasonable to reduce risk of

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	recurrent stroke. • To further reduce the risk of ASCVD in patients with severe hypertriglyceridemia (>500 mg/dL), patients should implement a low-fat diet, avoid refined carbohydrates and alcohol, and consume omega-3 fatty acids.
American Association of the Study of Liver Disease: **Primary Biliary Cholangitis (2018)[13] and Update (2021)[14]**	• Ursodeoxycholic acid (UDCA) at a dose of 13 to 15 mg/kg/day is the first-line therapy for primary biliary cholangitis (PBC). • UDCA is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage. • For patients requiring bile acid sequestrants, UDCA should be given at least one hour before or four hours after the bile acid sequestrant. • Biochemical response to UDCA should be evaluated at 12 months after treatment initiation to determine whether patients should be considered for second-line therapy. • Obeticholic acid (OCA) was approved by the Food and Drug Administration in May 2016 to be used in combination with UDCA in patients with PBC who have inadequate response to at least one year of treatment with UDCA, or as monotherapy for those patients who are intolerant to UDCA. • Patients who are inadequate responders to UDCA should be considered for treatment with OCA, starting at 5 mg/day. • Fibrates can be considered as off-label alternatives for patients with PBC and inadequate response to UDCA, although fibrates are discouraged in patients with decompensated liver disease. • Use of OCA and fibrates is discouraged in patients with decompensated liver disease (Child-Pugh-Turcotte B or C). • OCA is contraindicated in patients with advanced cirrhosis, defined as cirrhosis with current or prior evidence of liver decompensation or portal hypertension. • Cholestyramine, colestipol, and colesevelam are nonabsorbable, highly positively charged resins that bind to negatively charged anions such as bile acids. It is not known which substance in the gut they may be binding to that leads to improved cholestatic itching, and clinical trials proving their efficacy are limited, but they have a long track record of clinical use.
American Association of Clinical Endocrinologists: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)[15]**	<u>Principles of Comprehensive Type 2 Diabetes Management Algorithm</u> • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, ASCVD, congestive heart failure, chronic kidney disease, overweight/obesity, and nonalcoholic fatty liver disease. • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c is 6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets. • Get to goal as soon as possible (adjust 3 months). • Avoid hypoglycemia. • Continuous glucose monitoring is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. <u>ASCVD Risk Reduction Algorithm: Dyslipidemia</u> • Treatment of dyslipidemia is an essential component of diabetes mellitus and prediabetes management. • Unless contraindicated, a statin should be used as the first-line therapy for dyslipidemia in persons with type 2 diabetes. • In persons with type 2 diabetes, additional laboratory testing of lipid levels should be undertaken at frequent intervals (every 6 to 12 weeks) to direct titration of the statin or addition of an adjunct therapy in order to achieve lipid

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	targets; less frequent testing intervals can be considered once lipid goals are consistently achieved. • If lipid targets cannot be achieved with maximally tolerated statin therapy, then the addition of the cholesterol absorption inhibitor ezetimibe (10 mg/day) should be considered. • If treatment goals are not met on a maximally tolerated statin combined with ezetimibe, additional therapy with a bile acid sequestrant (colesevelam, colestipol, cholestyramine) or bempedoic acid (adenosine triphosphate-citrate lyase inhibitor) is an option. • In extreme risk patients with lipid values above targets on maximal high-intensity statin in combination with the above-mentioned add-on therapies, there may be a need for more aggressive therapy with a PCSK9 inhibitor or inclisiran, with consideration of approved indications and access. <u>Glucose-Centric Algorithm for Glycemic Control</u> • Metformin should be initiated if there is no contraindication. • In order to maximize tolerability, metformin should be started at a low dose and titrated over the course of a few weeks to the maximally tolerated dose. • Many individuals will require >1 antihyperglycemic medication to achieve their individualized A1C target over the course of the disease. • Clinicians should consider multiple factors when selecting the second agent, including presence of overweight or obesity, hypoglycemia risk, access/cost, and presence of severe hyperglycemia. • Patients often present with >1 of these factors, so using a patient-centered, shared decision-making approach is important. • In those patients with overweight or obesity and the additional goal of weight loss, dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, glucagon-like peptide-1 receptor agonist, or sodium glucose cotransporter 2 inhibitor class are preferred options. • Persons with a history of hypoglycemia, at high risk of hypoglycemia, and/or at risk for severe complications from hypoglycemia should preferentially be initiated with an agent associated with low risk for hypoglycemia, including glucagon-like peptide-1 receptor agonist, sodium glucose cotransporter 2 inhibitor, dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, thiazolidinedione, or dipeptidyl peptidase-4 inhibitor. • If titrated to maximum tolerable dose and not at glycemic target at ≤3 months, add best available agent not in use, including glucagon-like peptide-1 receptor agonist, dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, sodium glucose cotransporter 2 inhibitor, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, sulfonylurea/glinide, colesevelam, bromocriptine quick release or pramlintide.
National Institute for Health and Clinical Excellence: **Identification and management of familial hypercholesterolaemia (2008)[16]** **Last updated October 2019**	<u>Drug treatment in adults</u> • When offering lipid-modifying drug therapy to adults with familial hypercholesterolemia (FH), inform the patient that this treatment should be life-long. • Offer a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who would otherwise be initiated on statin therapy but who are unable to do so because of

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	contraindications or intolerance to initial statin therapy.
	• Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who have been initiated on statin therapy when:
	  ○ Serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy AND
	  ○ Consideration is being given to changing from initial statin therapy to an alternative statin.
	• Appropriate control of cholesterol concentrations should be based on individualized risk assessment according to national guidance on managing cardiovascular disease in the relevant populations.
	• Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist center.
	• Offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).
	• Offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are at a very high risk of a coronary event [i.e., they have established coronary heart disease, a family history of premature coronary heart disease, or two or more other cardiovascular risk factors (e.g. they are male, they smoke, or they have hypertension or diabetes)].
	• Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration.
	• The decision to offer treatment with a bile acid sequestrant (resin) or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH.
	• Exercise caution when adding a fibrate to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together.
	
	<u>Drug treatment in children and young people</u>
	• All children and young people diagnosed with, or being investigated for, a diagnosis of FH should have a referral to a specialist with expertise in FH in children and young people.
	• Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of ten years. The decision to defer or offer lipid-modifying drug therapy to a child or young person should take into account their age, the age of onset of coronary heart disease within the family, and the presence of other cardiovascular risk factors, including LCL-C concentration.
	• When offering lipid-modifying drug therapy for children or young people, inform the child/young person and their parent/caregiver that this treatment should be life-long.
	• Offer statins to children with FH by the age of ten years or at the earliest opportunity thereafter.
	• For children and young people with FH, consider a statin that is licensed for use in the appropriate age group.
	• Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group.
	• In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering:

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	○ A higher dose of statin than is licensed for use in the age group, and/or ○ More than one lipid-modifying drug therapy, and/or ○ Lipid-modifying drug therapy before the age of ten years. • In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy, and this should be considered before LDL apheresis. • In children and young people with FH who are intolerant of statins, consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration [such as bile acid sequestrants (resins), fibrates, or ezetimibe]. • Routine monitoring of growth and pubertal development in children and young people with FH is recommended.
American College of Cardiology: **Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2022)**[17]	• Provides recommendations for situations not covered by the 2018 ACC/AHA cholesterol guidelines and for whether or when to use non-statin therapies if response to statins is deemed inadequate. • For all patient groups, lifestyle modification (adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) is a critical component of ASCVD risk reduction. The clinician-patient discussion regarding the addition of a non-statin medication to the current medication regimen should address the potential for net ASCVD risk reduction, safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering, cost, convenience, and medication storage, pill burden, frequency and route of administration, potential to jeopardize adherence to evidence-based therapies and patient preference. <u>Adults With Clinical ASCVD on Statin Therapy for Secondary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider LDL apheresis under care of lipid specialist if baseline LDL-C ≥190 mg/dL not due to secondary causes without clinical or genetic diagnosis of familial hypercholesterolemia. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH under care of lipid specialist, if at very high risk and baseline LDL-C ≥190 mg/dL not due to secondary causes with clinical diagnosis or genetic confirmation of familial hypercholesterolemia. <u>Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Primary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH.
European Atherosclerosis Society/European Society of Vascular Medicine Joint Statement: **Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease (2021)**[18]	• Statins, at the highest tolerated dose, are indicated in patients with PAD for the prevention of cardiovascular events. • LCL-C should be lowered to <1.4 mmol/L and by >50% if pre-treatment values are 1.8 to 3.5 mmol/L. • Combination treatment with a statin and ezetimibe may be considered to improve LDL-C goal attainment. This approach could allow better tolerance of a lower dose of statin in patients with statin side-effects. • A PCSK9 inhibitor should be added if LDL-C levels remain 50% higher than goal despite statin treatment, with or without ezetimibe. • Antiplatelet therapy is indicated to prevent further cardiovascular events. This should either be clopidogrel 75 mg/day or the combination of aspirin 100 mg/day and rivaroxaban. • Dual antiplatelet therapy should be given for at least one month after drug coated balloon angioplasty, and for three months after either drug eluting or covered

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	stent implantation. • Combination therapy with aspirin and rivaroxaban should be considered for dual antiplatelet therapy post-intervention.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the bile acid sequestrants 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 Bile Acid Sequestrants[2-4,19]

Indication	Cholestyramine	Colesevelam	Colestipol
Hypercholesterolemia			
Adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia		✔	
Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated LDL-C) who do not respond adequately to diet	✔ *		
Adjunctive therapy to diet for the reduction of elevated serum total cholesterol and LDL-C in patients with primary hypercholesterolemia (elevated LDL-C) who do not respond adequately to diet			✔
Monotherapy or in combination with a statin to reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia who are unable to reach LDL-C target levels despite an adequate trial of dietary therapy and lifestyle modification		✔	
Miscellaneous			
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus		✔	
Relief of pruritus associated with partial biliary obstruction	✔		

*May be useful to lower LDL-C in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

IV. Pharmacokinetics

The pharmacokinetic parameters of the bile acid sequestrants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Bile Acid Sequestrants[2-4,20]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Cholestyramine	0	Not reported	None	Feces (100)	Not reported
Colesevelam	0	Not reported	None	Renal (0.05) Feces (majority; % not reported)	Not reported
Colestipol	0	Not reported	None	Renal (<0.05) Feces (100)	Not reported

V. Drug Interactions

Major drug interactions with the bile acid sequestrants are listed in Table 5.

Table 5. Major Drug Interactions with the Bile Acid Sequestrants[20]

Generic Name(s)	Interaction	Mechanism
Cholestyramine, Colesevelam, Colestipol	Bezafibrate	Concurrent use of bezafibrate and ion exchange resins may result in decreased bezafibrate efficacy.
Cholestyramine, Colesevelam, Colestipol	Deferasirox	Gastrointestinal absorption and enterohepatic recycling of deferasirox may be decreased due to the formation of physical chemical complexes with bile acid sequestrants. Plasma concentrations and pharmacologic effects of deferasirox may be decreased.
Cholestyramine, Colestipol	Digoxin	Concurrent use of bile acid sequestrants and digoxin may result in decreased digoxin levels.
Cholestyramine, Colesevelam, Colestipol	Mycophenolate	Concurrent use of bile acid sequestrants and mycophenolate mofetil may result in reduced mycophenolic acid exposure.

VI. Adverse Drug Events

The most common adverse drug events reported with the bile acid sequestrants are listed in Table 6. Cholestyramine and colestipol can decrease plasma folate levels with long-term administration; therefore, folic acid supplementation may be necessary.[2-4] Bile acid sequestrants may also decrease the absorption of fat-soluble vitamins A, D, E, and K.[2-4]

Table 6. Adverse Drug Events (%) Reported with the Bile Acid Sequestrants[2-4]

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Cardiovascular			
Angina	-	-	✔
Aortic stenosis	-	✔	-
Bradycardia	-	✔	-
Chest pain	-	-	✔
Hypertension	-	2.8	-
Myocardial infarction	-	✔	-
Tachycardia	-	-	✔
Central Nervous System			
Anxiety	✔	-	-
Dizziness	✔	-	✔
Drowsiness	✔	-	-
Fatigue	✔	3.9	✔
Femoral nerve pain	✔	-	-
Headache	✔	3.9 to 7.6	✔
Insomnia	-	-	✔
Light-headedness	-	-	✔
Migraine	-	-	✔
Paresthesia	✔	-	-
Syncope	✔	-	-
Tinnitus	✔	-	-
Vertigo	✔	-	-
Weakness	-	-	✔
Gastrointestinal			
Abdominal pain/discomfort	✔	-	✔

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Abdominal distention	-	-	-
Anorexia	✔	-	✔
Black stools	✔		✔
Bleeding from a known duodenal ulcer	✔	-	-
Bloating	✔	-	✔
Cholecystitis	-	-	✔
Cholelithiasis	✔	-	✔
Constipation	✔	3 to 11	✔
Diarrhea	✔	5	✔
Diverticulitis	✔	-	-
Dyspepsia	-	3.9 to 8.3	-
Dysphagia	✔	-	-
Eructation	✔	-	-
Flatulence	✔		-
Heartburn	-	-	✔
Hemorrhoidal bleeding	✔		✔
Hiccups	✔	-	-
Indigestion	-	-	✔
Intestinal gas	-	-	✔
Intestinal obstruction	✔	-	-
Malabsorption syndrome	✔	-	-
Nausea	✔	3.0 to 4.2	✔
Pancreatitis	✔	-	-
Peptic ulcer	-	-	✔
Rectal bleeding	✔		
Rectal pain	✔	-	-
Sour taste	✔	-	-
Steatorrhea	✔	-	-
Ulcer attack	✔		
Vomiting	✔	2.3	✔
Genitourinary			
Burnt odor to urine	✔	-	-
Diuresis	✔	-	-
Dysuria	✔	-	-
Hematuria	✔	-	-
Hematological			
Anemia	✔	-	-
Ecchymosis	✔		
Hypoprothrombinemia	✔	-	-
Ecchymosis	✔	-	-
Prolonged prothrombin time	✔	-	-
Laboratory Test Abnormalities			
Creatinine phosphokinase increased	-	2.3	-
Hypoglycemia	-	3	-
Liver function test abnormalities	✔	-	✔
Triglycerides increased	-	✔	-
Musculoskeletal			
Aches	-	-	✔
Arthritis	✔	-	✔
Backache	✔	-	✔
Joint pain	-	-	✔
Muscle and joint pain	✔	-	-
Myalgia	-	2.1	-
Osteoporosis	✔	-	-

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Pain	-	-	✔
Respiratory			
Nasopharyngitis	-	4.1 to 6.2	-
Pharyngitis	-	3.2	-
Rhinitis	-	2.3 to 3.2	-
Sinusitis	-	-	-
Upper respiratory tract infection	-	4.9	-
Other			
Accidental injury	-	3.7	-
Asthenia	-	3.6	-
Asthma	✔	-	-
Dental bleeding	✔	-	-
Dental caries	✔	-	-
Edema	✔	-	-
Erosion of tooth enamel	✔	-	-
Flu syndrome	-	3.2	-
Increased libido	✔	-	-
Influenza	-	3.8	-
Irritation of skin, tongue, perianal area	✔	-	-
Metabolic acidosis	✔	-	-
Rash	✔	-	✔
Shortness of breath	✔		✔
Swelling of hands or feet	-	-	✔
Swollen glands	✔	-	-
Tooth discoloration	✔	-	-
Urticaria	✔	-	✔
Uveitis	✔	-	-
Vitamin A deficiency	✔	-	-
Vitamin D deficiency	✔	-	-
Weight gain	✔	-	-
Weight loss	✔	-	-
Wheezing	✔		

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the bile acid sequestrants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Bile Acid Sequestrants[2-4,19]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Cholestyramine	Primary hyperlipidemia: Powder: initial, one packet or one level spoonful once or twice daily; maintenance, two to four packets or scoopfuls daily (8 to 16 g) divided into two doses; maximum, six packets or scoopfuls (24 g) daily Relief of pruritus associated with partial biliary obstruction: Powder: initial, one packet or one level spoonful once or twice daily;	Primary hyperlipidemia: Powder: although an optimal dosage schedule has not been established, standard texts list a usual pediatric dose of 240 mg/kg/day in two to three divided doses, normally not to exceed 8 g/day* Relief of pruritus associated with partial biliary obstruction:	Powder (for oral suspension): 4 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maintenance, two to four packets or scoopfuls daily (8 to 16 g) divided into two doses; maximum, six packets or scoopfuls (24 g) daily	Powder: although an optimal dosage schedule has not been established, standard texts list a usual pediatric dose of 240 mg/kg/day in two to three divided doses, normally not to exceed 8 g/day*	
Colesevelam	Primary hyperlipidemia (as monotherapy or in combination with an HMG CoA reductase inhibitor): Powder: one 3.75 g packet once daily Tablet: six tablets once daily or three tablets twice daily Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Powder: 3.75 g once daily Tablet: six tablets once daily or three tablets twice daily	Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Powder: one 3.75 g packet once daily Tablet: six tablets once daily or three tablets twice daily Safety and efficacy have not been established in children <10 years of age or in premenarchal girls. Due to tablet size, the oral suspension is recommended for use in the pediatric population.	Powder (for oral suspension): 3.75 g Tablet: 625 mg
Colestipol	Primary hyperlipidemia: Granules: one to six packets or level scoopfuls given once or in divided doses; initiate treatment with one dose once or twice daily with an increment of one dose/day at one- or two-month intervals Tablet: initial, 2 g once or twice daily; maintenance, 2 to 16 g/day administered once or in divided doses	Safety and efficacy in children have not been established.	Granules (for oral suspension): 5 g (Colestid®) 7.5 g (Colestid Flavored®)† Tablet: 1 g

*The effects of long-term administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients are unknown.
†One dose contains 5 g of colestipol hydrochloride.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the bile acid sequestrants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Bile Acid Sequestrants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Ballantyne et al.[21] (2004) Cholestyramine 16 g/day and rosuvastatin 80 mg/day vs rosuvastatin 80 mg/day	MC, OL, PG, RCT Adults ≥18 years of age with severe hypercholesterolemia (LDL-C 190 to 400 mg/dL) and fasting TG <400 mg/dL	N=147 12 weeks	Primary: Percent change in LDL-C from baseline to end of treatment Secondary Percent change from baseline in LDL-C after 6 weeks of 40 mg rosuvastatin; percent change from baseline at 6 and 12 weeks of rosuvastatin treatment for: TC, HDL-C, TG, apo AI, apo B, lipid ratios (LDL:HDL) and inflammatory markers (CRP, IL6); compliance	Primary: At 12 weeks, no significant difference between the groups was seen: the rosuvastatin group had an LDL-C reduction of 56.4% and rosuvastatin with cholestyramine group had an LDL-C reduction of 60.5% (P<0.08). Secondary: LDL-C reductions were 52.2% after treatment with 40 mg rosuvastatin. Other measurements, TC, HDL-C, TG, apo B, apo AI and lipid ratios were not significantly different between the groups (P=0.20, 0.71, 0.47, 0.75, 0.53, 0.17, respectively). Decreases in CRP were 29% after six weeks, 42% after rosuvastatin 80 mg and 48% after rosuvastatin 80 mg with cholestyramine. 49% of patients in the cholestyramine group were not compliant with the cholestyramine treatment.
Eriksson et al.[22] (1998) Cholestyramine 16 g/day vs	MC, RCT Men and women, aged 30 to 65 years old	N=2,036 12 months	Primary: Reduction in LDL-C Secondary: Compliance	Primary: Percent change in LDL-C from baseline to end point was as follows: cholestyramine -26% (95% CI, -23 to -29), cholestyramine and pravastatin -36% (95% CI, -33 to -39), pravastatin (20 mg) -27% (95% CI, -25 to -29), pravastatin (40 mg) -32% (95% CI, -30 to -34). Secondary: Compliance rates with each regimen were as follows: cholestyramine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cholestyramine 8 g/day and pravastatin 20 mg/day vs pravastatin 20 mg/day vs pravastatin 40 mg/day				44%, cholestyramine and pravastatin 53%, pravastatin (20 mg) 76%, and pravastatin (40 mg) 78%. Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common in the cholestyramine group and the cholestyramine with pravastatin group.
Davidson et al.[23] (2010) Colesevelam 0.75 g BID, titrated up to a maximum of 1.875 g BID If a 15 to 30% LDL-C reduction was not achieved with the maximum colesevelam dose by week 12, low dose statin or niacin therapy could be added.	ES, OL Patients ≥18 years of age with primary hypercholesterolemia (LDL-C ≥160 mg/dL and TG ≤300 mg/dL)	N=260 50 weeks	Primary: Mean change from baseline in LDL-C Secondary: Mean percent change from baseline in LDL-C; mean change and mean percent change from baseline in TC, TG and HDL-C; safety	Primary: Colesevelam monotherapy or combination therapy resulted in significant mean LDL-C level reduction of 29.6 mg/dL (from 185.8 to 156.2 mg/dL), corresponding to a mean 15.0% reduction from baseline (P<0.00 for both). Secondary: Colesevelam reduced the mean TC level from baseline to week 50 (270.2 to 258.3 mg/dL) by 11.9 mg/dL (4.0%; P<0.001). The median TG level increased from baseline to week 50 (145.5 to 165.0 mg/dL) by 13.0 mg/dL (10.3%). The median HDL-C level increased from baseline to week 50 (49.5 to 54.0 mg/dL) by 5.0 mg/dL (10.8%; P<0.001). Twenty three patients discontinued colesevelam due to treatment-emergent adverse events. Treatment-emergent adverse events were reported by 225 patients (86.5%), with the majority of adverse events (74.7%) classified as mild to moderate in severity. The most common adverse events included infection (28.5%), constipation (16.5%), flatulence (13.5%) and general pain (13.1%).
Rosenson et al.[24] (2006) Colesevelam 1.5 to 3.75 g/day	DB, MC, PC, RCT Hypercholesterolemia patients, LDL-C >160 mg/dL, average age of	N=137 6 weeks	Primary: LDL particle size and LDL particle number	Primary: Mean LDL particle size increased significantly in the group receiving colesevelam 3.75 g/day (P=0.01). Mean LDL particle number decreased significantly in the group receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	56 years old		Secondary: Not reported	colesevelam 3.75 g/day by 13.7% (P=0.0002). Mean LDL particle number decreased significantly in the group receiving colesevelam 3.0 g/day by 6.8% (P=0.03). Secondary: Not reported
Bays et al.[25] (2006) Colesevelam 3.75 g/day vs placebo	MA (3 trials) Patients ≥18 years of age with LDL-C 100 mg/dL to 250 mg/dL, TG ≤300 mg/dL and on stable doses of statin therapy, either atorvastatin, pravastatin or simvastatin for ≥4 weeks	N=204 6 weeks	Primary: Mean percent change in LDL-C level from baseline to end point Secondary: HsCRP, absolute and percent change in HDL-C, TC, apo AI, apo B, TG, and absolute change in HsCRP; safety (measured by incidence of treatment-emergent adverse events)	Primary: Patients receiving colesevelam with a statin had significantly greater reductions in LDL-C than those receiving placebo plus a statin at the end of the study (P<0.01 for absolute difference; P≤0.001 for % treatment difference). Secondary: HsCRP levels decreased significantly as compared to placebo when colesevelam was combined with simvastatin or pravastatin (P=0.0154 and P=0.0279, respectively). Patients receiving colesevelam with a statin did not have a significant increase in HDL-C as compared to those receiving placebo plus a statin at the end of the study (P>0.05). Patients receiving colesevelam with a statin had significantly greater reductions in TC than those receiving placebo plus a statin at the end of the study (P<0.05). Apo B levels were not significantly different. No serious drug-related adverse events were reported. The incidence of drug-related adverse events was higher in the groups receiving colesevelam with a statin (13 to 26%) than placebo with a statin (0 to 13%).
Huijgen et al.[26] (2010) Colesevelam 3,750 mg/day	DB, PC, RCT Patients 18 to 75 years of age with familial hyper-cholesterolemia	N=86 12 weeks	Primary: Percent change from baseline to week six in LDL-C	Primary: The between-group difference in change from baseline LDL-C was significant at week six, with an least squares means change of -18.5% (95% CI, -25.3 to -11.8)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients were receiving ezetimibe/ simvastatin.	refractory to treatment		Secondary: Percentage change from weeks six to 12 in HDL-C, TC, TG, apo A1, apo B, apo B/A1; percentage change from baseline to week 12 in LDL-C; proportion of patients achieving an LDL-C target of ≤2.5 mmol/L at weeks six and 12; proportion of patients with a decrease from baseline in LDL-C ≥15% at weeks six and 12; absolute changes in fasting glucose, HbA_{1c}, and hsCRP at weeks six and 12	Secondary: Between group differences (95% CI) in LDL-C, TC, HDL-C, TG and apo B/A1 after 12 weeks were -12.0 (-17.8 to -6.3), -7.3 (-12.0 to -2.6), 3.3 (-2.4 to 9.0), 2.8 (-10.4 to 15.9) and -12.2% (-20.2 to -4.2). Mean TC concentrations were significantly reduced with colesevelam compared to placebo at weeks six and 12 (least squares means between-group differences, -11.1 and -7.3%; *P*<0.001 and *P*<0.003). On average, TG levels increased with colesevelam from baseline to weeks six and 12. There was no significant group differences in HDL-C at week six and 12 (*P* values not reported). The difference in the proportions of patients who achieved the target LDL-C (≤2.5 mmol/L) with colesevelam and placebo was not significant (9 vs 3%; *P* value not reported). The proportion of patients who achieved ≥15% reduction in LDL-C at week six was significantly higher with colesevelam (32 vs 0%; *P*<0.001). This difference remained significant at week 12 (30 vs 8%; *P*=0.012). Although not significant at week six (-0.06%), the least squares means between-group difference in change from baseline to week 12 in mean HbA_{1c} concentration was significant (-0.12%; *P*=0.027). There were no significant between-group differences in fasting glucose or hsCRP at week six and 12.
Stein et al.[27] (2010) Colesevelam 1.875 g/day vs colesevelam 3.75 g/day vs	DB, PC, PG, RCT Patients 10 to 17 years of age with heFH, TC >160 mg/dL who were naïve to cholesterol lowering therapy or LDL-C >130 mg/dL who were on a statin	N=194 32 weeks	Primary: Percent change in LDL-C from baseline Secondary: Percent change in non-HDL-C, adverse events	Primary: Treatment with colesevelam 3.75 and 1.875 g/d led to a significant reduction in LDL-C (-12.5%; P<0.001) and (-6.3%; P=0.031), respectively, compared to placebo at week 8. Reductions in LDL-C were observed for statin-naïve (-10.6%; P<0.001) or statin non-naïve patients (-20.2%; P=0.031) receiving colesevelam 3.75 g/day compared to placebo. The mean change in LDL-cholesterol was -9.3% (P<0.001) from week 8 to week 26. Those who received placebo had the greatest change in mean LDL-C (-14.5%; P<0.001), followed by patients receiving 1.875 g/day (-11.6%; P<0.001) and 3.75 g/day colesevelam (-1.9%; P=0.482). Reductions in LDL-cholesterol were also observed for statin-naïve and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				statin-stable patients, and patients who either changed or added a statin. Those treated with colesevelam 3.75 g/day resulted in a mean reduction from baseline in LDL-cholesterol of -14.0% (P<0.001) across all patients. Secondary: Treatment with colesevelam 3.75 g/day resulted in a reduction in TC (-7.4%; P=0.001), non-HDL-C (-10.9%; P=0.0001), apo B (-8.3%; P=0.0009), HDL-C (6.1%; P=0.008), and apo AI (6.9%; P=0.006) at week 8. There was no significant difference in TG among the treatment groups (P=0.466). Individuals receiving colesevelam 3.75 g/day also experienced clinically significant mean reductions in TC (-8.0%; P<0.001), non-HDL-C (-11.3%; P<0.001), and apo B (-11.3%; P<0.001), clinically significant increases in mean HDL-Cl (8.1%; P<0.001) and apo AI (5.6%; P<0.001), and a median increase in triglycerides (11.5%; P<0.001) at week 32.
Insull et al.[28] (2001) Colesevelam 2.3 g vs colesevelam 3.0 g vs colesevelam 3.8 g vs colesevelam 4.5 g vs placebo	DB, MC, PC, RCT Patients with primary hypercholesterolemia, LDL-C levels between 130-220 mg/dL	N=467 32 weeks	Primary: Mean absolute change in LDL-C from baseline to the end of 24-week treatment Secondary: Mean percent change in LDL-C, mean absolute and percent change in TC, apo B, apo AI, and median absolute change and percent change in HDL-C and TG	Primary: All doses of colesevelam resulted in significant absolute and percent change decreases in LDL-C at the end point as compared to placebo (P<0.001 for all). Absolute change decreases and percent decreases in LDL-C for the 2.3, 3.0, 3.8, and 4.5 g doses were 14 (9%), 19 (12%), 24 (15%), and 28 mg/dL (18%). Secondary: All doses of colesevelam resulted in significant reductions of TC (P<0.001). Absolute change decreases and percent decreases in TC for the 2.3, 3.0, 3.8, and 4.5 g doses were 10 (4%), 15 (6%), 18 (7%) and 24 mg/dL (10%). All doses of colesevelam resulted in significant increases in HDL-C (P<0.001). Absolute changes (increases) and percent increases in TC for the 2.3, 3.0, 3.8, and 4.5 g doses were 2 (3%), 2 (4%), 2 (3%) and 2 mg/dL (3%). All doses of colesevelam resulted in significant reductions in apo B relative to baseline (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Changes in apo AI and lipoprotein did not result in significant changes relative to baseline, except the 2.3 and 3.0 g doses resulted in significant changes in apo AI (P=0.02 and 0.03, respectively) TG levels did not change significantly as compared to placebo, however increases, 5 to 10%, were seen within groups from baseline to end point (P<0.05).
Hunninghake et al.[29] (2001) Colesevelam 3.8 g vs atorvastatin 10 mg vs colesevelam 3.8 g/day and atorvastatin 10 mg/day vs atorvastatin 80 mg/day vs placebo	DB, MC, PC, RCT Patients with elevated LDL-C levels ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change in LDL-C Secondary: Change in TC, HDL-C, TG, apo B, apo AI and lipoprotein(a) from baseline	Primary: All treatment groups resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions were -12% in the colesevelam 3.8 g group, -38% in the atorvastatin 10 mg group, -48% in the colesevelam 3.8 g and atorvastatin 10 mg group and -53% for the atorvastatin 80 mg group (P<0.05, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Secondary: Colesevelam 3.8 g/day reduced TC -6% (P<0.05), increased HDL-C 3% (P<0.05), and increased TG 10%. Atorvastatin 10 mg reduced TC -27% (P<0.0001), increased HDL-C 8% (P<0.05), and reduced TG -24% (P<0.05). Colesevelam 3.8 g and atorvastatin 10 mg reduced TC -31% (P<0.0001), increased HDL-C 11% (P<0.05), and reduced TG -1%. Atorvastatin 80 mg reduced TC -39% (P<0.0001), increased HDL-C 5% (P<0.05), and reduced TG -33% (P<0.0001). Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam 3.8 g with atorvastatin 10 mg. No significant differences in HDL-C were found between the groups. Apo B levels decreased significantly for all groups relative to baseline (P<0.01). No significant changes in Apo AI and lipoprotein were reported.
Davidson et al.[30]	DB, MC, PC, RCT	N=135	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Colesevelam 2.3 g vs lovastatin 10 mg vs colesevelam 2.3 g and lovastatin 10 mg taken together vs colesevelam 2.3 g and lovastatin 10 mg taken apart vs placebo	Patients with elevated LDL-C levels	4 week	Percent change in LDL-C Secondary: Changes in TC, HDL-C, TG, apo B	Colesevelam 2.3 g and lovastatin 10 mg together significantly reduced LDL-C 34% (-60 mg/dL; P<0.0001). Colesevelam 2.3 g and lovastatin 10 mg apart significantly reduced LDL-C 32% (-53 mg/dL; P<0.0001). Lovastatin 10 mg reduced LDL-C 22% (-39 mg/dL). Colesevelam 2.3 g reduced LDL-C 7% (-13 mg/dL). Both combination treatments were more effective than either treatment alone (P<0.05). Secondary: Both combination treatments resulted in reductions in TC by 21% and apo B by 24% (P<0.0001 for each). No significant effect on HDL-C or TG was found for the combination treatments.
Knapp et al.[31] (2001) Colesevelam 2.3 g vs colesevelam 3.8 g vs simvastatin 10 mg vs	DB, MC, PC, RCT Men and women, age 18 years and older, with elevated LDL-C levels, ≥160 mg/dL and TG ≤300 mg/dL and not taking cholesterol-lowering medication	N=258 6 weeks	Primary: Change in serum LDL-C from baseline to end point Secondary: Percent change in LDL-C, mean and percent change in TC, HDL-C, TG, apo B and apo AI from baseline	Primary: LDL-C serum changes were -7 mg/dL in the placebo group, -31 mg/dL in the colesevelam 3.8 g group, -48 mg/dL in the simvastatin 10 mg group -80 mg/dL in the colesevelam 3.8 g and simvastatin 10 mg group, -17 mg/dL in the colesevelam 2.3 g group, -61 mg/dL in the simvastatin 20 mg group and -80 mg/dL for the colesevelam 2.3 g and simvastatin 20 mg group (P<0.05, P<0.0001, P<0.0001, P<0.0001, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Secondary: LDL-C percent changes were -4% in the placebo group, -16% in the colesevelam 3.8 g group,-26% in the simvastatin 10 mg group, -42% in the colesevelam 3.8 g and simvastatin 10 mg group, -8% in the colesevelam 2.3 g group, -34% in the simvastatin 20 mg group and -42% for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 20 mg vs colesevelam 3.8 g and simvastatin 10 mg vs colesevelam 2.3 g and simvastatin 20 mg vs placebo				colesevelam 2.3 g and simvastatin 20 mg group (P<0.05, P<0.0001, P<0.0001, P<0.0001, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Significant changes from baseline were found for all treatment groups in mean and percent change in TC (P<0.0001 for all except colesevelam 2.3 g for which P<0.05). Significant changes from baseline were found for mean and percent change in HDL-C for simvastatin 10 mg (P<0.05), colesevelam 3.8 g with simvastatin 10 mg (P<0.0001), colesevelam 2.3 g (P<0.05), simvastatin 20 mg (P<0.05), and colesevelam 2.3 g with simvastatin 20 mg (P<0.05). Significant changes from baseline were found for mean and percent change in TG for colesevelam 3.8 g (P<0.05), simvastatin 10 mg (P<0.05), simvastatin 20 mg (P<0.05), and colesevelam 2.3 g with simvastatin 20 mg (P<0.05). Significant reductions from baseline for apo B were found for all groups. Reductions were significant (P<0.05) compared to placebo for all treatment groups except colesevelam 2.3 g. Significant increases in apo AI were seen in all treatment groups except simvastatin 10 mg (P<0.05).
Romanelli et al.[32] (2013) Colesevelam treatment (previous drug therapies remained in place)	RETRO New colesevelam users ≥ 18 years of age as of index date, diagnosis of hypercholesterolemia, ≥12 months of colesevelam treatment	Hypercholesterolemia: N=468 with 12 months of follow-up; N=181 with 24 months of follow-up Additional diagnosis of	Primary: Changes in LDL-C and percentage of patients at LDL-C goal; Among patients with diabetes mellitus (DM), changes in glycated hemoglobin (HBA_{1C}) and percentage of	Primary: LDL-C decreased significantly from baseline by a mean of 11.4 mg/dL and 15.7 mg/dL (P<0.0001, for each) at 12 and 24 months, respectively, and the percentages of patients at LDL-C goal increased by 13.9% and 21.0%. Among patients with DM and a baseline HBA_{1C} ≥8%, HBA_{1C} decreased significantly by a mean of 0.72% (P=0.0001) and 0.75% (P=0.010), and 11.5 and 12.8% were at HBA_{1C} goal at 12 and 24 months, respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
		diabetes: N=113 with 12 months of follow-up; N=39 with 24 months of follow-up	patients at HBA_{1C} goal Secondary: Not reported	
Davidson et al.[33] (2013) Colesevelam 3,750 mg vs placebo All patients took niacin at highest tolerated dose (up to 2000 mg)	PC, RCT Patients ≥18 years of age, with dyslipidemia (non–HDL-C ≥100 and ≤220 mg/dL), HDL-C <60 mg/dL, and FPG ≥90 mg/dL and ≤145 mg/dL	N=140 12 weeks	Primary: LDL-C Secondary: FPG, HDL-C, non–HDL-C, and TGs	Primary: The LDL-C reduction from baseline with colesevelam (-20.67%) was significantly greater than placebo (-12.86%; P=0.0088). Secondary: Both groups experienced increased HDL-C levels (between group difference P=0.879). Non–HDL-C levels decreased to a greater extent in the colesevelam group than in the placebo group (−17.92 vs −13.08%, respectively; P=0.0983). TG levels were also decreased in both groups (−15.2 and −10.3%, respectively; P=0.096). Total cholesterol levels were decreased in both groups (−3.94 and −7.44%, respectively; P=0.1203).
Blankernhorn et al.[34] (1987) Colestipol 30 g/day plus niacin 3 to 12 g/day vs placebo	DB, PC, RCT Nonsmoking men 49 to 59 years of age with progressive atherosclerosis who had coronary bypass surgery not involving valve replacement performed ≥3 months prior and a fasting blood cholesterol level 185 to 350 mg/dL	N=188 2 years	Primary: Coronary global change score Secondary: Change from baseline in lipid parameters	Primary: Deterioration in overall coronary status was significantly less with combination therapy compared to placebo (P<0.001). Atherosclerosis regression, as indicated by perceptible improvement in overall coronary status, occurred in 16.2 and 2.4% of patients receiving combination therapy and placebo (P=0.002). Combination therapy resulted in a significant reduction in the average number of lesions per patient that progressed (P<0.03) and the percentage of patients with new atheroma formation in native coronary arteries (P<0.03). The percentage of patients receiving combination therapy with new lesions (P<0.04) or any adverse change in bypass grafts (P<0.03) was significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reduced. Secondary: Large, significant decreases in TC (26 vs 4%), TG (22 vs 5%), LDL-C (43 vs 5%) and LDL-C/HDL-C (57 vs 6%), and a large, significant increase in HDL-C (37 vs 2%) were achieved with combination therapy compared to placebo (P<0.001 for all). Modifications in lipid parameters achieved with combination therapy were significant compared to baseline values (P values not reported).
Brown et al.[35] (2009) Colestipol 5 to 10 g TID plus niacin 125 mg BID titrated to 1 to 1.5 g TID vs Colestipol 5 to 10 g TID plus lovastatin 20 mg BID titrated to 40 mg BID vs placebo (or colestipol if LDL-C was elevated)	DB, RCT Men ≤62 years of age with elevated apo B and a family history of CAD	N=120 32 months	Primary: Average change in the percent stenosis for the worst lesion in each of the nine proximal segments Secondary: Average changes in all lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	Primary: On average, placebo (conventional therapy) increased the index of stenosis by 2.1 percentage points a baseline of 34%. By contrast, it decreased by 0.7 percentage points with colestipol plus lovastatin and by 0.9 percentage points with colestipol and niacin (P<0.003 for trend). At trial end, on average, these nine lesions were almost 3 percentage points less severe among patients treated intensively compared to conventionally. This difference represents almost 1/10 of the amount of disease present at baseline (34% stenosis). Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease when looking at the effect of treatment on certain subsets of lesions (all lesions measured in each patient, lesions causing severe or mild stenosis and those that did not cause total occlusion at baseline). The results with both treatment groups were significantly difference from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.
Primary Prevention of Cardiovascular Events				
The Lipid Research Clinics Coronary Primary Prevention Trial[36,37]	DB, MC, RCT Asymptomatic males with primary hypercholesterolemia,	N=3,806 7.4 years average	Primary: CHD death and/or nonfatal MI Secondary:	Primary: The cholestyramine group had a 19% reduction in risk of CHD death or nonfatal MI compared to placebo (P<0.05). Secondary

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1984) Cholestyramine vs placebo	following a moderate cholesterol-lowering diet		TC and LDL-C changes, incidence rates of: positive stress tests, angina, coronary bypass surgery	The cholestyramine group had a reduction in TC of 13.4% and a reduction in LDL-C of 20.3%. The placebo group had a TC reduction of 4.9% and a LDL reduction of 7.7%. Incidence rates of positive stress tests, angina and coronary bypass surgery were decreased in the cholestyramine group by 25, 20, and 21%, respectively.
Type 2 Diabetes Mellitus				
Rosenstock et al.[38] (abstract) (2010) Colesevelam 3.75 g/day vs placebo All patients received OL metformin 850 mg/day, titrated at week 2 to 1,700 mg/day.	DB, PC, RCT Adult patients with type 2 diabetes (HbA_{1c} 6.5 to 10.0%) and hypercholesterolemia (LDL-C ≥100 mg/dL)	N=286 16 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in LDL-C, TC, non-HDL-C, apo B, hsCRP, apo A-1 and TG; proportion of patients who achieved recommended treatment goals; safety and tolerability	Primary: Mean HbA_{1c} was reduced by 1.1 and 0.8% with colesevelam (from 7.8% at baseline to 6.6% at trial end) and placebo (from 7.5 to 6.7% at trial end), resulting in a treatment difference of -0.3% at trial end (P=0.0035). Secondary: Colesevelam significantly reduced LDL-C (-16.3%), TC (-6.1%), non-HDL-C (-8.3%), apo B (-8.0%) and hsCRP (-17%) (P<0.01 for all). Colesevelam significantly increased apo A-1 (4.4%) and TG (18.6%) compared to placebo (P<0.01 for all). The proportion of patients who achieved recommended goals with colesevelam compared to placebo, respectively, were as follows: HbA_{1c} <7; 67 vs 56% (P=0.0092), LDL-C <100 mg/dL; 48 vs 18% (P<0.001) and composite HbA_{1c} <7% plus LDL-C <100 mg/dL; 40 vs 12 (P<0.001). Safety and tolerability were similar between the two treatment groups.
Rosenson et al.[39] (2009) Colesevelam 3.75 g/day vs placebo	DB, PC, RCT Patients with type 2 diabetes who were receiving antihyperglycemic therapy (metformin, sulfonylurea, or both)	N=65 12 weeks	Primary: Effects on atherogenic lipoprotein subclasses (LDL-P, VLDL-P, IDL-P Secondary: Not reported	Primary: Colesevelam therapy was associated with a change in HbA_{1c} of -0.3% compared to a change of 0.2% in the placebo group (P=0.007). The mean percentage change in LDL-C was -9.6% in the colesevelam group compared to 2.1% in the placebo group (P=0.007). The mean percentage change in apo B was -6.3% (in the colesevelam group compared to 5.5% in the placebo group (P=0.003). There was no significant difference in TG (P=0.570) or HDL-C (P=0.585) among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean percent reduction in LDL-P was -15.5% (P=0.006) with colesevelam. The mean percent change of total atherogenic lipoproteins (LDL-P, IDL-P and VLDL-P) was reduced by -14.2% in colesevelam-treated patients (P=0.011 vs placebo). Secondary: Not reported
Zieve et al.[40] (2007) GLOWS Colesevelam 3.75 g/day vs placebo	DB, PC, PG, PRO, RCT Patients diagnosed with type 2 diabetes, an A1C 7.0%-10.0%, and on a stable dose of a sulfonylurea and/or metformin as their only antidiabetic agent for ≥90 days	N=65 12 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Changes in fructosamine levels, FPG levels, postprandial glucose level, meal glucose response (difference between pre and postprandial glucose levels) % change in lipids: LDL, TC, TG, apo AI and B	Primary: The change in HbA_{1c} from baseline to 12 weeks for the colesevelam group was -0.3% and for placebo 0.2%, for a treatment difference of 0.5% (P=0.007). For patients with a baseline HbA_{1c} ≥8.0, there was a greater difference in HbA_{1c}, -1.0%, after 12 weeks of treatment (P=0.002). The reduction in HbA_{1c} in the treatment groups did not differ based on oral antidiabetic treatment. Secondary: Significantly lower FPG was seen in the colesevelam group at weeks 4 and 8, (P=0.016, P=0.011), but not at week 12. Significantly lower fructosamine levels were seen in the colesevelam group at week 12 (P=0.011). Significantly lower postprandial glucose levels were seen in the colesevelam group at week 12 (P=0.026). No significant difference was seen in meal glucose response (P=0.195). Significantly lower lipid parameters, including LDL, TC, apo B and LDL particle concentration, were seen in the colesevelam group as compared to placebo (P=0.007, P=0.019, P=0.003, and P=0.037, respectively).
Bays et al.[41] (2008)	DB, PC, PG Patients aged 18-75	N=316 26 weeks	Primary: Mean change from baseline in HbA_{1c}	Primary: Colesevelam reduced mean HbA_{1c} by 0.39% compared to a 0.15% increase with placebo (P<001). The treatment difference was observed as

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Colesevelam 3.75 g/day vs placebo	years with inadequately controlled type 2 diabetes mellitus taking a stable dose of metformin monotherapy or metformin in combination with other oral anti-diabetic medications (sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and/or meglitinides)		level Secondary: Mean change in HbA_{1c}, FPG, fructosamine levels, reduction in FPG >30 mg/dL or HbA_{1c} >0.7%, C-peptide, adiponectin, insulin levels, TC, LDL-C, HDL-C, non–HDL-C, TG, apo AI, apo B, TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, apo B:apo AI, hsCRP	early as week 6 (P<001). Secondary: Colesevelam added to metformin monotherapy reduced HbA_{1c} by -0.44% compared to an increase of 0.02% with placebo (P=0.002). Colesevelam added to metformin in combination with other oral anti-diabetic drugs reduced HbA_{1c} by -0.35% compared to an increase of 0.27% with placebo (P<001). Colesevelam reduced FPG compared to placebo (-13.9 mg/dL; P=0.01), with a significant treatment difference observed at week 6 (-20.8 mg/dL; P<001). Colesevelam reduced fructosamine level compared to placebo (-23.2 µmol/L; P<0.001), with a significant treatment difference reported by 6 weeks (-25.5 µmol/L; P<0.001). Altogether, 47.7% of patients in the colesevelam group and 35.5% of patients in the placebo group experienced either a reduction in FPG >30 mg/dL or HbA_{1c} >0.7% (P=0.03). A greater percentage of patients in the colesevelam group compared to placebo achieved a reduction in HbA_{1c} >0.7% (38.3 vs 20.4%, respectively; P<0.001). Colesevelam did not produce a significant treatment difference for C-peptide compared to placebo (-0.1 ng/mL; P=0.54). Colesevelam was not associated with a significant treatment difference in adiponectin (-0.3 µg/mL; P=0.52), insulin (-0.9 µIU/mL; P=0.51), or the HOMA index (-0.3; P=0.68). Compared to placebo, colesevelam reduced LDL-C, TC, non–HDL-C, and apo B levels (P<0.001 for all). There was no significant difference in HDL-C, TG or apo AI between the treatment groups. Treatment with colesevelam led to a greater reduction in hsCRP compared to placebo (-14.4%; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fonseca et al.[42] (2008) Colesevelam 3.75 g/day vs placebo	DB, PC, PG Adults with type 2 diabetes mellitus that were inadequately controlled on a stable dose of sulfonylurea alone or in combination with additional oral antidiabetes agents for at least 90 days	N=461 26 weeks	Primary: Mean change in HbA_{1c} Secondary: FPG, fructosamine, C-peptide, mean change in A1C for the sulfonylurea monotherapy and sulfonylurea combination therapy cohorts; percentage of patients achieving a reduction in FPG ≥30 mg/dl or A1C ≥0.7%; lipids, lipoproteins, and lipid and lipoprotein ratios; high-sensitivity C-reactive protein (hsCRP)	Primary: Colesevelam reduced HbA_{1c} by -0.32%, whereas placebo increased A1C by 0.23% (P<0.001). Secondary: Colesevelam significantly lowered FPG compared to placebo (-13.5 mg/dl; P<0.009), with a difference observed as early as 6 weeks (-13.7 mg/dl; P<0.001). A significant difference in fructosamine was reported with colesevelam compared to placebo (-21.4 µmol/l; P<0.001). There was no significant difference in C-peptide among the treatment groups (P=0.102). A similar effect on HbA_{1c} was observed in the sulfonylurea monotherapy group (-0.79%; P<0.001) and the sulfonylurea combination therapy (-0.42%; P<0.001) groups. A significantly greater percentage of patients in the colesevelam group achieved an HbA_{1c} reduction ≥0.7% compared to placebo (35.2 vs 16.5%, respectively; P<0.001). There was a significantly greater number of individuals in the colesevelam group who achieved either a reduction in HbA_{1c} ≥0.7% or a reduction in FPG ≥30 mg/dl compared to placebo (47.5 vs 32.1%, respectively; P=0.001). Significant treatment differences in LDL-C, non–HDL-C, TC, TG, apo AI, and apo B were observed after 26 weeks of treatment with colesevelam compared to placebo (P<0.001 for all). The least squares mean percent change in LDL-C from baseline to week 26 (LOCF) was -16.1% in the colesevelam group and 0.6% in the placebo group (-16.7%; P<0.001). There was no significant difference in HDL-C among the treatment groups (P=0.916). Significant treatment differences between colesevelam and placebo were reported in TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, and apo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				B:apo AI (P≤0.003 for all). There was no significant difference in hsCRP among the treatment groups (P=0.063).
Goldberg et al.[43] (2008) Colesevelam 3.75 g/day vs placebo	DB, MC, PC, PG, PRO Patients 18 to 75 years of age with type 2 diabetes not adequately controlled with insulin alone or in combination with oral antidiabetes agents (a biguanide, a biguanide sulfonylurea combination, a sulfonylurea, a thiazolidinedione, or a meglitinide)	N=287 16 Weeks	Primary: Mean change in HbA_{1c} Secondary: FPG, fructosamine, HbA_{1c}, percentage of patients achieving a reduction in FPG ≥30 mg/dl or HbA_{1c} ≥0.7%, C-peptide, TC, LDL-C, HDL-C, non–HDL-C, TG, apo AI, apo B, TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, apo B:apo AI, hsCRP	Primary: The mean change in the HbA_{1c} was -0.41% in the colesevelam group and 0.09% in the placebo group (P<.001). Secondary: There was no significant difference in FPG among the treatment groups (P=0.08). Colesevelam significantly decreased mean fructosamine levels compared to placebo (P<0.001). Approximately 48.6% of patients in the colesevelam group and 31.6% of patients in the placebo group had a reduction in the FPG level >30 mg/dL or a reduction in the HbA_{1c} of >0.7% (P=0.004). More than twice as many patients in the colesevelam-treated group had a reduction in the HbA_{1c} level of 0.7% or greater compared to those in the placebo group (34.7% vs 14.0%; P<001). However, no significant difference was noted in the percentage of individuals achieving a reduction in FPG level of 30 mg/dL or higher between the colesevelam treated and placebo groups at week 16. Mean change from baseline in C-peptide levels was similar in both groups. No significant least squares mean treatment difference was evident at week 16 LOCF (P=0.65). Colesevelam resulted in a significantly greater percentage reduction in LDL-C compared to placebo (P<0.001). The median percent change and median change in triglycerides for the colesevelam and placebo groups were 22.7 vs 0.3% and 32.0 vs -1.3 mg/dL, respectively (P<0.001 for both). Treatment with colesevelam significantly reduced apo B levels by 5.3% compared to placebo (P=0.04), but did not result in a significant increase in apo AI. Colesevelam led to a significant decrease in LDL-C:HDL-C and apo B:apo AI, but not in the TC:HDL-C or non– HDL-C:HDL-C.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in hsCRP among the treatment groups (P=0.13).
Goldfine et al.[44] (2010) Colesevelam 3.75 g/day vs placebo	ES, OL Patients 18 to 75 years of age with type 2 diabetes who were inadequately controlled on insulin-based therapy, metformin-based therapy or sulfonylurea-based therapy	N=509 52 weeks	Primary: Safety and tolerability Secondary: Change in HbA_{1c} and FPG, percent change in lipid and lipoprotein levels, change in lipid ratios, percentage of patients who achieved either a reduction in HbA_{1c} ≥0.7% or FPG ≥30 mg/dL, percentage of patients who achieved HbA_{1c} <7.0%	Primary: During the extension, 70.9% of patients experienced an adverse event. The majority (88.1%) were mild or moderate in severity. Fifty-six patients (11%) experienced a drug-related adverse event. Most drug-related adverse events were gastrointestinal (constipation and flatulence) in nature. Thirty five (6.9%) discontinued use due to an adverse event; 16 patients (3.1%) discontinued due to a drug-related adverse event. Fifty-four patients (10.6%) had a serious adverse drug reaction; only one was considered to be drug related; 12 patients (2.4%) discontinued the drug due to a serious event. Seventeen patients (3.3%) reported an episode of hypoglycemia; most were considered mild and two were considered moderate severity. Secondary: Treatment with colesevelam reduced the HbA_{1c} by -0.6% compared to -0.1% with placebo. At week 52, 14.1% of patients achieved HbA_{1c} <7.0% and 26.9% of patients had a reduction in HbA_{1c} of ≥0.7%. One-hundred-twenty-six patients (24.8%) achieved a reduction in FPG ≥30 mg/dl from baseline A at 52 weeks. Improvements in mean LDL-C with colesevelam were maintained. Both groups that received colesevelam had sustained effects over time. Baseline A had lipid and lipoprotein levels were nearly the same between colesevelam and placebo. By the conclusion of the double-masked study (baseline B), the individuals that received colesevelam had reduced mean levels of LDL-C, non-HDL-C, TC, and apo B, and increased mean levels of HDL-C, median levels of TG, and mean levels of apo AI relative to baseline (baseline A). For those who received colesevelam in the double-masked study, the lipid effects were maintained through the extension. For those who received colesevelam in the 52-week extension, mean LDL-C, non-HDL-C, TC and apo B levels decreased while mean HDL-C, median TG, and mean apo A-I levels increased.
Jialal et al.[45]	DB, PC, RCT (Pooled	N=1,018	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Colesevelam 3.75 g/day vs placebo	analysis of 3 trials) Patients 18 to 75 years of age with type 2 diabetes who were inadequately controlled on insulin-based therapy, metformin-based therapy or sulfonylurea-based therapy	16 to 26 weeks	Glycemic and lipid effects Secondary: Lipid effects on those patients on concomitant statin treatment	Mean HbA_{1c} was significantly reduced with colesevelam compared to placebo (-0.54%; P<0.0001). Mean FPG was significantly reduced with colesevelam vs placebo (-15.1 mg/dL; P<0.0001). Colesevelam therapy resulted in a significant reduction in TC and LDL-C compared to placebo (-5.15 and -15.3%, respectively; P<0.0001). TG was significantly increased in the colesevelam group relative to placebo (15.0%; P<0.0001). Non-HDL-C and apo B were reduced with colesevelam vs placebo (-6.80 and -6.6%, respectively; P<0.0001). There was no significant effect on HDL-C between the two groups. Apo AI levels increased significantly in the colesevelam group relative to placebo (2.8%; P<0.0001). Median levels of hsCRP were significantly reduced with colesevelam relative to placebo treatment (-0.4 mg/L; P=0.0009). Secondary: Colesevelam treatment resulted in a significant decrease in HbA_{1c} (-0.45%; P<0.0001) and LDL-C (-15.6%; P<0.0001) in patients on statin therapy at baseline.
Bays (abstract).[46] (2011) Colesevelam 3.75 g/day vs placebo	Post hoc analysis of 3 DB, PC, RCT Patients with type 2 diabetes receiving metformin, sulfonylurea, or insulin monotherapy or combination therapy as part of their background therapy	N=696 26 weeks	Primary: Change in baseline HbA_{1c}, change in baseline lipid parameters Secondary: Safety	Primary: Compared to placebo, colesevelam significantly reduced HbA_{1c} and FPG (mean treatment difference, -0.5% and -15.7 mg/dL, respectively; *P*<0.001 for both). Compared to placebo, colesevelam significantly reduced LDL-C (mean treatment difference, -16.5%), TC (-5.8%), non-HDL-C (-8.2%), and apo B (-7.6%) (P<0.0001 for all). Median TG levels (median treatment difference, 12.8%; P<0.0001) and mean apo AI levels (mean treatment difference, 3.3%; P<0.0001) were increased with colesevelam. There was an increase in HDL-C with colesevelam, compared to placebo, that was not significant (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Colesevelam was generally well tolerated.
Aggarwal et al.[47] (2012) Colesevelam vs placebo	MA (8 clinical trials) Patients with type 2 diabetes	N=1,038 Duration not specified	Primary: Change in baseline FPG, HbA_{1c}, LDL-C, HDL-C, TG, and TC Secondary: Not reported	Primary: Compared to placebo, there was a significant reduction in FPG with colesevelam (OR, -0.302; 95% CI, -0.448 to -0.156). Compared to placebo, there was a significant reduction in HbA_{1c} with colesevelam (OR, -0.594; 95% CI, -0.747 to -0.442). Compared to placebo, there was a significant reduction in LDL-C with colesevelam (OR, -1.346; 95% CI, -2.411 to -0.279). Compared to placebo, there was an insignificant reduction in TC with colesevelam (OR, -0.487; 95% CI, -1.641 to 0.667). Compared to placebo, there was a significant increase in TG with colesevelam (OR, -0.300; 95% CI, 0.0130 to 0.587). Secondary: Not reported
Bajaj et al.[48] (2020) GOAL-RCT Colesevelam 3.75 g daily vs ezetimibe 10 mg daily	OL, MC, RCT Patients with type 2 diabetes mellitus >6 months, HbA_{1c} of 7.1% to 10.0%, LDL-c >2.0 mmol/L, stable diabetes medications for at least 3 months (with the exception of allowance for change in insulin dose), and a stable dose of statin (or alternative lipid-lowering) therapy for a minimum of 3 months	N=200 24 weeks	Primary: Proportion of participants achieving an LDL-C target of ≤2.0 mmol/L and HbA_{1c} target of ≤7.0% Secondary: Changes in glucose and cholesterol laboratory values	Primary: The primary composite outcome was achieved by similar proportions of participants with colesevelam (14.6%) and ezetimibe (10.5%) ($P_{non\text{-}inferiority}<0.001$, $P_{superiority}=0.41$). Secondary: LDL-C reduction from baseline was less with colesevelam compared with ezetimibe (14.0% vs. 23.2%, P<0.01), as was the proportion of subjects achieving an LDL-C target of ≤2.0 mmol/L (47.6% and 67.0%, respectively; P=0.007). Mean HbA_{1c} was reduced with colesevelam (-0.26 ± 0.10%), while no change was observed with ezetimibe (difference P=0.06). Adverse events and discontinuation rates were higher for colesevelam (20.2% and 31.1%) compared with ezetimibe (7.2% and 6.2%), respectively.
Rigby et al.[49] (2010)	OL	N=169	Primary: Change in HbA_{1c}	Primary: At week 16, HbA_{1c} was reduced from baseline in all treatment groups (LS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosiglitazone 4 mg/day (QD or BID) and metformin (existing therapy) vs sitagliptin 100 mg QD and metformin (existing therapy) vs colesevelam 3.75 g/day (QD or BID) and metformin (existing therapy)	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 ≥60 mg/dL and TGs <500 mg/dL	16 weeks	from baseline to week 16 Secondary: Change in HbA_{1c} from baseline to week eight, change in FPG and fasting 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%	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 sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109). FPG was significantly reduced from baseline at week eight and week 16 in all treatment groups. The two-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups. There was no significant change in fasting insulin or 2-hour postprandial insulin from baseline to week 16 in any treatment group. 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). 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). 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<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect TG levels. HDL-C levels did not change significantly from baseline with any treatment. At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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%. 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.

Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial
Miscellaneous abbreviations: apo=apolipoprotein, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, CRP=C-reactive protein, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, heFH=heterozygous familial hypercholesterolemia, HOMA=homeostasis model assessment, hsCRP=high-sensitivity C-reactive protein, IDL-P=intermediate-density lipoprotein particle, IL6=interleukin 6, LDL-C=low density lipoprotein cholesterol, LDL-P=low density lipoprotein particle, LOCF=last observation carried forward, MI=myocardial infarction, TC=total cholesterol, TG=triglycerides, VLDL-C=very low density lipoprotein cholesterol

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 Bile Acid Sequestrants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cholestyramine	packet for oral suspension, powder for oral suspension	Questran®*†, Questran Light®*‡	$$$	$$
Colesevelam	packet for oral suspension, tablet	Welchol®*	$$$$$	$$
Colestipol	granules for oral suspension, packet for oral suspension, tablet	Colestid®*	$$$$$	$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The bile acid sequestrants are approved as an adjunct to diet and exercise to reduce total cholesterol and low-density lipoprotein cholesterol (LDL-C). In addition, cholestyramine is indicated to relieve pruritus associated with partial biliary obstruction.[2-4,19] Colesevelam is also indicated for the treatment of type 2 diabetes mellitus. Bile acid sequestrants can lower LDL-C by 15 to 30% and raise high-density lipoprotein cholesterol (HDL-C) by 3 to 5%. Serum triglyceride levels may increase or remain unchanged.[1] All agents are available in a generic formulation.

In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant, or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels and are recommended in patients with established coronary heart disease or coronary heart disease equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy.[1,5-8,11] American College of Cardiology/American Heart Association released updated guidelines in 2013 which support initiating a statin in patients with established atherosclerotic cardiovascular disease (ASCVD). According to these recommendations, percent reduction in LDL-C is an indicator of response and adherence to therapy, but treating to a targeted level is not a primary goal.[9] Combination therapy can be considered on an individual basis, but studies of combination therapy have generally not shown benefit beyond statin monotherapy. Additionally, if patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.[9] The 2018 American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol recommend using an LDL-C threshold of 70 mg/dL to consider the addition of non-statins to statin therapy in very high-risk ASCVD patients.[8]

Pruritus is a complication of primary biliary cirrhosis and bile acid sequestrants are the drug of choice for the treatment of this complication.[13] With regards to the use of bile acid sequestrants in the management of patients with type 2 diabetes, the 2023 American Association of Clinical Endocrinologists algorithm, notes that if treatment goals for dyslipidemia are not met on maximally tolerated statin combined with ezetimibe, additional therapy with a bile acid sequestrant or bempedoic acid is an option. The algorithm also lists colesevelam as a treatment option if preferred and alternative glycemic control agents are titrated to maximum tolerable dose and glycemic target is not achieved at ≤3 months.[15] Guidelines do not give preference to one bile acid sequestrant over another.[1,5-18]

Clinical trials have demonstrated that the bile acid sequestrants can effectively lower LDL-C, non-HDL-C, and total cholesterol and positively impact other lipid/lipoprotein parameters.[21-49] There are few trials that directly compare the efficacy and safety of these agents. Treatment with cholestyramine led to a 19% reduction in the risk of fatal and non-fatal myocardial infarction in the Lipid Research Clinics Coronary Primary Prevention Trial.[36,37] Positive cardiovascular outcomes have also been detected in clinical trials which combined bile acid sequestrants with other lipid-modifying drugs.[1] The efficacy of combination therapy with colesevelam and a DPP-4 inhibitor has not been evaluated for the treatment of type 2 diabetes.[2] When added to existing diabetic regimens, colesevelam lowered the glycosylated hemoglobin by 0.3 to 0.6% compared to the addition of placebo.[40-49]

There is insufficient evidence to support that one brand bile acid sequestrant 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 bile acid sequestrants 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 bile acid sequestrant 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cholesterol Absorption Inhibitors
AHFS Class 240605
February 7, 2024

I. Overview

The antilipemic agents are categorized into six different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, HMG-CoA reductase inhibitors (statins), and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Ezetimibe is the only cholesterol absorption inhibitor that is currently available. It inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe can lower low-density lipoprotein cholesterol by about 18%.[1]

The cholesterol absorption inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ezetimibe is available in a generic formulation. This class was last reviewed in February 2022.

Table 1. Cholesterol Absorption Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ezetimibe	tablet	Zetia®*	ezetimibe

PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cholesterol absorption inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cholesterol Absorption Inhibitors

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[2]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins.

Clinical Guideline	Recommendation
	• In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)[3]**	<u>General recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant, or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Statins</u> • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. <u>Bile acid sequestrants</u> • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients

Clinical Guideline	Recommendation
	needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. <u>Nicotinic acid</u> • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout, and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <u>Fibric acid derivatives (fibrates)</u> • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <u>Omega-3 fatty acids</u> • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2017)[4] and**	<u>Cholesterol Goals</u> • For patients at low risk for ASCVD (i.e., no risk factors), goals of LDL-C<130 mg/dL, non-HDL-C<160 mg/dL, and TG<150 mg/dL are recommended. • For patients at moderate risk for ASCVD (i.e., two or fewer risk factors and a calculated 10-year risk of <10%), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at high risk for ASCVD (i.e., two or more risk factors and a 10-year risk between 10% and 20% or who have diabetes or stage ≥3 CKD with no other risk factors), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at very high risk for ASCVD (i.e., established clinical ASCVD or recent hospitalization for ACS, carotid or peripheral vascular disease, or 10-year

Clinical Guideline	Recommendation
Executive Summary (2020)[5]	risk >20%; diabetes with one or more risk factor(s); CKD stage 3 or higher with albuminuria; or HeFH), goals of LDL-C<70 mg/dL, non-HDL-C<100 mg/dL, apo B<80 mg/dL, and TG<150 mg/dL are recommended. • For individuals at extreme risk (i.e., progressive ASCVD including unstable angina that persists after achieving an LDL-C <70 mg/dL; established clinical ASCVD in individuals with diabetes, CKD stage 3 or higher, and/or HeFH); history of premature ASCVD (<55 years of age for males or <65 years of age for females), goals of LDL-C<55 mg/dL, non-HDL-C<80 mg/dL, apo B<70 mg/dL, and TG<150 mg/dL are recommended. • An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100 to 129 mg/dL considered "borderline" and 130 mg/dL or greater considered "high" (based on recommendations from the American Academy of Pediatrics). • Due to its potential cardioprotective role, HDL-C should be >40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C. <u>General Recommendations</u> • A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes and patient education with pharmacotherapy as needed to achieve evidence based targets. • A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include ≥30 minutes of moderate-intensity physical activity [consuming 4 to 7 kcal/min] four to six times weekly, with an expenditure of ≥200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities. • Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs. • In addition to aerobic activity, muscle-strengthening activity is recommended at least two days a week. • For adults, a reduced-calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains (primarily whole grains), fish, and lean meats is recommended. • For adults, the intake of saturated fats, trans-fats, and cholesterol should be limited, while LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10 to 25 g/day). • Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children. • Excessive alcohol intake should be avoided. • Tobacco cessation should be strongly encouraged and facilitated. • In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals. <u>Statins</u> • Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. • For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction.

Clinical Guideline	Recommendation
	• In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered. • Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, who also have at least one additional risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL. • Extreme risk individuals should be treated with statins to target an even lower LDL-C treatment goal of <55 mg/dL. <u>Fibrates</u> • Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). • Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add fibrate. • In patients treated with a statin and icosapent ethyl with TG≥150 mg/dL, a fibrate may be considered. <u>Omega-3 Fish Oil</u> • Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose. • Omega-3 should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add omega-3. <u>Niacin</u> • Niacin therapy is recommended principally as an adjunct for reducing TG. • Niacin therapy should not be used in individuals aggressively treated with statin due to absence of additional benefits with well-controlled LDL-C. • Niacin should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add niacin. • In patients treated with a statin and icosapent ethyl with TG>150 mg/dL, niacin may be considered. <u>Icosapent Ethyl</u> • Icosapent ethyl (two grams twice daily) should be added to a statin in any patient with established ASCVD or diabetes with two or more ASCVD risk factors and triglycerides between 135 to 499 mg/dL to prevent ASCVD events. <u>Bile Acid Sequestrants</u> • Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG. <u>Cholesterol Absorption Inhibitors</u> • Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals.

Clinical Guideline	Recommendation
	• Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk. PCSK9 Inhibitors • Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH. • PCSK9 inhibitors should be considered in patients with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals. Combination Therapy • Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal. Special Considerations: Women • Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient. • Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended. Special Considerations: Children and Adolescents • Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, and particularly for those satisfying the following criteria: o LDL-C ≥190 mg/dL o LDL-C ≥160 mg/dL and the presence of two or more cardiovascular risk factors, even after vigorous intervention o Family history of premature ASCVD (before 55 years of age), or o Having overweight, obesity, or other elements of the insulin resistance syndrome Follow-up and Monitoring • Reassess individuals' lipid status six weeks after therapy initiation and again at six-week intervals until the treatment goal is achieved. • While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals. • While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment. • More frequent lipid status evaluation is recommended in situations such as deterioration of diabetes control, use of a new drug known to affect lipid levels, progression of atherothrombotic disease, considerable weight gain, unexpected adverse change in any lipid parameter, development of a new ASCVD risk factor, or convincing new clinical trial evidence or guidelines that suggest stricter lipid goals. • Liver transaminase levels should be measured before and three months after niacin or fibric acid treatment initiation because most liver abnormalities occur within 3 months of treatment initiation. Liver transaminase levels should be measured periodically thereafter (e.g., semiannually or annually). • Creatine kinase levels should be assessed and the statin discontinued, at least temporarily, when an individual reports clinically significant myalgias or muscle

Clinical Guideline	Recommendation
	weakness on statin therapy.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (2018)[6]**	<u>Top 10 messages to reduce risk of atherosclerotic cardiovascular disease through cholesterol management</u> • In all individuals, emphasize a heart-healthy lifestyle across the life course. • In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. ○ Clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin. • In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy. Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. • In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. • In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. • In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 to 189 mg/dL (≥1.8 to 4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium (CAC). • Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement four to 12 weeks after statin initiation or dose adjustment, repeated every three to 12 months as needed. <u>Recommendations for Statin Therapy Use in Patients With ASCVD</u> • In patients who are 75 years of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. • In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels. • In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe. • In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost. • In patients with clinical ASCVD who are on maximally tolerated statin therapy

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	and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy. • In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences. • In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. • In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe. • In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (three to five years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events. <u>Recommendations for primary severe hypercholesterolemia (LDL-C ≥190 mg/dL)</u> • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher, maximally tolerated statin therapy is recommended. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher, ezetimibe therapy is reasonable. • In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL, who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL, while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered. • In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. • In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher and who achieve an on-treatment LDL-C level of 130 mg/dL or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. <u>Recommendations for patients with diabetes mellitus</u> • In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. <u>Primary prevention recommendations for adults 40 to 75 years of age with LDL levels 70 to 189 mg/dL</u> • In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more. • For the primary prevention of clinical ASCVD in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL, the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%),

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	intermediate-risk (≥7.5% to <20%), and high-risk (≥20%). • Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision. • In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy. • In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND o If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); o If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥ 55 years of age; o If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy • In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin. • In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Recommendations for older adults</u> • In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL, initiating a moderate-intensity statin may be reasonable. • In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy. • In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL, it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy. <u>Recommendations for children and adolescents</u> • In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity. • In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C. • In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL or higher with a clinical presentation consistent with familial hypercholesterolemia (FH) and who do not respond adequately with three to six months of lifestyle therapy, it is reasonable to initiate statin therapy. • In children and adolescents with a family history of either early CVD or significant hypercholesterolemia, it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age two years to detect FH or rare forms of hypercholesterolemia. • In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when

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	possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia. • In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome. • In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of nine and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities. <u>Recommendations for hypertriglyceridemia</u> • In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides. • In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy. • In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy. • In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL, and especially fasting triglycerides ≥1000 mg/dL), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy. <u>Recommendations for statin safety and statin-associated side effects</u> • A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully. • In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors. • In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and SAMS, is recommended before initiation of treatment. • In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy. • In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss. • In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase

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	(hepatic panel) if there are symptoms suggesting hepatotoxicity. • In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks. • In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit. • Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS. • In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[7]	<u>Statin treatment</u> • The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. • For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to

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	75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%. • Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. • Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. • Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age. • Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. • Creatine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). • Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes

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	mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug). • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant

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	of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. • In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. <u>Non statin safety</u> • Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. • Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. • In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. • To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. • Bile acid sequestrants should not be used in individuals with baseline fasting

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	triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. • A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. • It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. • It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. • Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. • Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. • Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. • If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)[8]**	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication

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	is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND ○ If the coronary artery calcium score is zero, it is reasonable to withhold

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	statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary

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	prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2021)**[9]	Drugs • Currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins), fibrates, bile acid sequestrants, selective cholesterol absorption inhibitors (e.g. ezetimibe) and, more recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and bempedoic acid. Response to all therapy varies widely among individuals and therefore monitoring the effect on LDL-C levels is recommended. • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins also lower triglycerides, and may reduce pancreatitis risk. • Statins should be used as the drugs of first choice in patients at increased risk of ASCVD. • Selective cholesterol absorption inhibitors (ezetimibe) should be considered as second-line therapy, either on top of statins when the therapeutic goal is not achieved, or when a statin cannot be prescribed. • Among patients in whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C levels when administered in combination with ezetimibe. • PCSK9 inhibitors also lower triglycerides, raise HDL-C and apolipoprotein A-I, and lower lipoprotein(a), although the relative contributions of these lipid modifications remain unknown. • PCSK9 inhibitors decrease LDL-C by up to 60%, either as monotherapy or in addition to the maximal statin dose or other lipid-lowering therapies (ezetimibe). • Fibrates are used primarily for triglyceride lowering and, occasionally, for increasing HDL-C. Evidence supporting the use of these drugs for CVD event reduction is limited and, given the strong evidence favoring statins, routine use of these drugs in CVD prevention is not recommended. In order to prevent pancreatitis, when triglycerides are >10 mmol/L (>900 mg/dL) they must be reduced not only by drugs but also by restriction of alcohol, treatment of DM, withdrawal of estrogen therapy, etc. In those rare patients with severe primary hypertriglyceridemia, specialist referral must be considered. Recommendations for pharmacological low-density lipoprotein cholesterol lowering for those <70 years of age • It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group. • If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. • For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered. • For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge),

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	ezetimibe should be considered. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may be considered. • If the goal is not achieved, statin combination with a bile acid sequestrant may be considered.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2021)[10]**	Secondary Stroke Prevention • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or transient ischemic attack (TIA) presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other clinical ASCVD. • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, and LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD. • Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2018 ACC/AHA cholesterol guidelines, which include lifestyle modifications, dietary recommendations, and medication recommendations. Treatment of Hypertriglyceridemia • In patients with ischemic stroke or TIA with fasting TG 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL, on moderate or high-intensity statin, with HbA_{1c} <10%, and with no history of pancreatitis, AF, or severe heart failure, treatment with icosapent ethyl (IPE) 2 g twice a day is reasonable to reduce risk of recurrent stroke. • To further reduce the risk of ASCVD in patients with severe hypertriglyceridemia (>500 mg/dL), patients should implement a low-fat diet, avoid refined carbohydrates and alcohol, and consume omega-3 fatty acids.
American Association of the Study of Liver Disease: **Primary Biliary Cholangitis (2018)[11] and Update (2021)[12]**	• Ursodeoxycholic acid (UDCA) at a dose of 13 to 15 mg/kg/day is the first-line therapy for primary biliary cholangitis (PBC). • UDCA is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage. • For patients requiring bile acid sequestrants, UDCA should be given at least one hour before or four hours after the bile acid sequestrant. • Biochemical response to UDCA should be evaluated at 12 months after treatment initiation to determine whether patients should be considered for second-line therapy. • Obeticholic acid (OCA) was approved by the Food and Drug Administration in May 2016 to be used in combination with UDCA in patients with PBC who have inadequate response to at least one year of treatment with UDCA, or as monotherapy for those patients who are intolerant to UDCA. • Patients who are inadequate responders to UDCA should be considered for treatment with OCA, starting at 5 mg/day. • Fibrates can be considered as off-label alternatives for patients with PBC and inadequate response to UDCA, although fibrates are discouraged in patients with decompensated liver disease. • Use of OCA and fibrates is discouraged in patients with decompensated liver disease (Child-Pugh-Turcotte B or C). • OCA is contraindicated in patients with advanced cirrhosis, defined as cirrhosis with current or prior evidence of liver decompensation or portal hypertension. Cholestyramine, colestipol, and colesevelam are nonabsorbable, highly positively charged resins that bind to negatively charged anions such as bile acids. It is not known which substance in the gut they may be binding to that leads to improved cholestatic itching, and clinical trials proving their efficacy are limited, but they

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	have a long track record of clinical use.
National Institute for Health and Clinical Excellence: **Identification and management of familial hypercholesterolaemia (2008)[13]** **Last updated October 2019**	Drug treatment in adults • When offering lipid-modifying drug therapy to adults with familial hypercholesterolemia (FH), inform the patient that this treatment should be life-long. • Offer a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications or intolerance to initial statin therapy. • Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who have been initiated on statin therapy when: o Serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy AND o Consideration is being given to changing from initial statin therapy to an alternative statin. • Appropriate control of cholesterol concentrations should be based on individualized risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. • Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist center. • Offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). • Offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are at a very high risk of a coronary event [i.e., they have established coronary heart disease, a family history of premature coronary heart disease, or two or more other cardiovascular risk factors (e.g. they are male, they smoke, or they have hypertension or diabetes)]. • Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration. • The decision to offer treatment with a bile acid sequestrant (resin) or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH. • Exercise caution when adding a fibrate to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together. Drug treatment in children and young people • All children and young people diagnosed with, or being investigated for, a diagnosis of FH should have a referral to a specialist with expertise in FH in children and young people. • Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of ten years. The decision to defer or offer lipid-modifying drug therapy to a child or young person should take into account their age, the age of onset of coronary heart disease within the family, and the presence

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	of other cardiovascular risk factors, including LCL-C concentration. • When offering lipid-modifying drug therapy for children or young people, inform the child/young person and their parent/caregiver that this treatment should be life-long. • Offer statins to children with FH by the age of ten years or at the earliest opportunity thereafter. • For children and young people with FH, consider a statin that is licensed for use in the appropriate age group. • Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group. • In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering: o A higher dose of statin than is licensed for use in the age group, and/or o More than one lipid-modifying drug therapy, and/or o Lipid-modifying drug therapy before the age of ten years. • In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy, and this should be considered before LDL apheresis. • In children and young people with FH who are intolerant of statins, consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration [such as bile acid sequestrants (resins), fibrates, or ezetimibe]. • Routine monitoring of growth and pubertal development in children and young people with FH is recommended.
American College of Cardiology: **Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2022)**[14]	• Provides recommendations for situations not covered by the 2018 ACC/AHA cholesterol guidelines and for whether or when to use non-statin therapies if response to statins is deemed inadequate. • For all patient groups, lifestyle modification (adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) is a critical component of ASCVD risk reduction. The clinician-patient discussion regarding the addition of a non-statin medication to the current medication regimen should address the potential for net ASCVD risk reduction, safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering, cost, convenience, and medication storage, pill burden, frequency and route of administration, potential to jeopardize adherence to evidence-based therapies and patient preference. <u>Adults With Clinical ASCVD on Statin Therapy for Secondary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider LDL apheresis under care of lipid specialist if baseline LDL-C ≥190 mg/dL not due to secondary causes without clinical or genetic diagnosis of familial hypercholesterolemia. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH under care of lipid specialist, if at very high risk and baseline LDL-C ≥190 mg/dL not due to secondary causes with clinical diagnosis or genetic confirmation of familial hypercholesterolemia. <u>Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Primary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH.
European	• Statins, at the highest tolerated dose, are indicated in patients with PAD for the

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Atherosclerosis Society/European Society of Vascular Medicine Joint Statement: **Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease (2021)**[15]	prevention of cardiovascular events. • LCL-C should be lowered to <1.4 mmol/L and by >50% if pre-treatment values are 1.8 to 3.5 mmol/L. • Combination treatment with a statin and ezetimibe may be considered to improve LDL-C goal attainment. This approach could allow better tolerance of a lower dose of statin in patients with statin side-effects. • A PCSK9 inhibitor should be added if LDL-C levels remain 50% higher than goal despite statin treatment, with or without ezetimibe. • Antiplatelet therapy is indicated to prevent further cardiovascular events. This should either be clopidogrel 75 mg/day or the combination of aspirin 100 mg/day and rivaroxaban. • Dual antiplatelet therapy should be given for at least one month after drug coated balloon angioplasty, and for three months after either drug eluting or covered stent implantation. • Combination therapy with aspirin and rivaroxaban should be considered for dual antiplatelet therapy post-intervention.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cholesterol absorption 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 Cholesterol Absorption Inhibitors[1]

Indication	Ezetimibe
Adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia	✔
Adjunctive therapy to diet for the reduction of elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with primary hyperlipidemia	✔
Administered in combination with a HMG-CoA reductase inhibitor (statin), as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, apo B, and non-HDL-C in patients with primary hyperlipidemia	✔
Administered in combination with fenofibrate, as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, apo B, and non-HDL-C in adult patients with mixed hyperlipidemia	✔
Administered in combination with simvastatin or atorvastatin for the reduction of elevated TC and LDL-C levels in patient with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the cholesterol absorption inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cholesterol Absorption Inhibitors[16]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ezetimibe	Not reported	>90	Intestine (extensive; % not reported); Liver (% not reported)	Renal (11) Feces (78)	19 to 30

V. Drug Interactions

Major drug interactions with the cholesterol absorption inhibitors are listed in Table 5.

Table 5. Major Drug Interactions with the Cholesterol Absorption Inhibitors[16]

Generic Name(s)	Interaction	Mechanism
Ezetimibe	Clofibrate	Concurrent use of clofibrate and ezetimibe may result in increased risk of cholelithiasis.
Ezetimibe	Gemfibrozil	Concurrent use of ezetimibe and gemfibrozil may result in increased ezetimibe concentrations and an increased risk of cholelithiasis.

VI. Adverse Drug Events

The most common adverse drug events reported with the cholesterol absorption inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Cholesterol Absorption Inhibitors[1]

Adverse Events	Ezetimibe
Central Nervous System	
Depression	✔
Dizziness	✔
Fatigue	1.6 to 2.4
Headache	✔
Paresthesia	✔
Dermatologic	
Erythema multiforme	✔
Rash	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain	✔
Diarrhea	2.2 to 4.1
Nausea	✔
Hematologic	
Thrombocytopenia	✔
Laboratory Test Abnormalities	
Creatine phosphokinase increased	✔
Liver transaminases increased	1
Musculoskeletal	
Arthralgia	2.4 to 3.0
Back pain	2.3
Myalgia	3.2 to 3.7
Myopathy	✔
Pain in extremities	1.9 to 2.7
Rhabdomyolysis	✔
Respiratory	
Coughing	2.3
Nasopharyngitis	3.3 to 3.7
Sinusitis	2.8
Upper respiratory tract infection	2.8 to 4.3
Other	
Anaphylaxis	✔
Angioedema	✔
Cholecystitis	✔
Cholelithiasis	✔

Adverse Events	Ezetimibe
Hepatitis	✔
Hypersensitivity reactions	✔
Influenza	2.0 to 2.1
Pancreatitis	✔

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the cholesterol absorption inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Cholesterol Absorption Inhibitors[1,17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ezetimibe	Homozygous familial hypercholesterolemia: Tablet: 10 mg once daily Homozygous sitosterolemia: Tablet: 10 mg once daily Primary hypercholesterolemia: Tablet: 10 mg once daily	Heterozygous familial hypercholesterolemia in children ≥10 years of age: 10 mg once daily Safety and efficacy in children <10 years of age and in premenarchal girls have not been established.	Tablet: 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cholesterol absorption inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Cholesterol Absorption Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Pearson et al.[18] (2006) Ezetimibe 10 mg QD Patients either received ezetimibe as monotherapy, in combination with a low-dose statin (20 mg/day or less of atorvastatin or its equivalent), or in combination with a high-dose statin (20 mg/day or more of atorvastatin or its equivalent).	Cohort, RETRO Men and women ≥18 years old who took ezetimibe for a minimum of two weeks	N=84 2 to 6 weeks	Primary: Change in fasting lipid profile at baseline to 2 to 6 weeks of ezetimibe therapy, clinical effectiveness results stratified by primary vs secondary prevention Secondary: Percentage of patients able to achieve their LDL-C target levels in accordance with their calculated Framingham risk category and defined Canadian guidelines and safety and tolerability	Primary: The mean reductions from baseline to two to six weeks of ezetimibe therapy were: TC 1.11mmol/L (16.5%), LDL-C level 1.01 mmol/L (22.3%), and ratio of TC:HDL 0.68 mmol/L (12.8%) (P<0.001 for all). The HDL-C level increased by 0.06 mmol/L (4.6%) from baseline to two to six weeks of ezetimibe therapy (P<0.001). Results were similar when stratified by primary (n=28) vs secondary (n=56) prevention. Among the primary prevention group, only the TC levels, LDL-C levels and TC:HDL ratio reductions were statistically significant (P<0.001). In the secondary prevention group, the reductions in TC levels, LDL-C levels, HDL-C levels and TC:HDL ratio all achieved statistical significance (P<0.001). LDL-C level reductions from baseline, stratified by drug regimen, were -1.03 mmol/L (-20.5%) for ezetimibe monotherapy, -1.19 mmol/L (-30.1%) for ezetimibe and a low-dose statin, and -0.95 mmol/L (-22.5%) for ezetimibe plus a high-dose statin (P<0.001 for ezetimibe monotherapy and ezetimibe plus a high-dose statin; P=0.0017 for ezetimibe plus a low-dose statin). Secondary: There were seven patients out of 34 (20.6%) in the ezetimibe monotherapy group, five out of 12 (41.6%) in the ezetimibe plus low-dose statin group and 18 out of 38 (47.4%) in the ezetimibe plus high-dose statin group who achieved previously unattainable target LDL-C levels. There were four patients who discontinued therapy due to treatment-related adverse event.
Jelesoff et al.[19] (2006) Ezetimibe 10	RETRO Patients who received ezetimibe as add-on	N=53 Not reported	Primary: TC, LDL-C, TG, HDL-C	Primary: The addition of ezetimibe resulted in reductions of 18, 25, and 17% (P<0.001) for TC, LDL-C, and TG, respectively. There were no significant differences in HDL-C (P value not significant).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day All patients were receiving niacin.	therapy to stable doses of niacin and other lipid medications		Secondary: Percent change in patients meeting NCEP ATP III treatment guidelines	 Secondary: Thirteen percent of patients met goals prior to addition of ezetimibe while 45% of patients met goals following addition of ezetimibe (P<0.001).
Simons et al.[20] (2007) EASY Ezetimibe 10 mg QD All patients were receiving statin therapy.	OL Men and women from Australia, mean age 65.6 years, with CHD or diabetes mellitus who had already used ≥40 mg/day of a statin for ≥3 months with current TC of >4 mmol/L for existing CHD or >6.5 mmol/L for diabetes or >5.5 mmol/L for diabetes if HDL-C is <1.0 mmol/L	N=130 6 weeks	Primary: LDL reduction and percentage of patients who reached LDL goal of <2.5 mmol/L or <2.0 mmol/L and other lipid parameters Secondary: Not reported	Primary: The LDL-C levels after six weeks were reduced by 29% (95% CI, 25 to 34) in patients receiving ezetimibe. Goal LDL-C of <2.5 and <2.0 mmol/L were reached by 70 and 50% of patients receiving ezetimibe (95% CI, 59 to 79 and 39 to 60, respectively). TC and TG levels were reduced by 19 and 11%, respectively, in patients receiving ezetimibe (95% CI, -21 to -16 and -16 to -5). There were no significant changes in HDL-C observed (95% CI, 0 to 6). Secondary: Not reported
Bissonnette et al.[21] (2006) Ezetimibe 10 mg QD All patients were receiving statin therapy.	MC, OL, PRO Men and women ≥18 years of age with a confirmed diagnoses of hypercholesterolemia and elevated plasma LDL-C levels of ≥2.5 mmol/L for patients at high 10-year CAD risk, ≥3.5 mmol/L for patients at moderate 10-year CAD risk and ≥4.5 mmol/L for patients at low 10-year	N=953 6 weeks	Primary: Percentage of change in LDL-C during the 6 week treatment period Secondary: Percentage of patients who had achieved the recommended target LDL-C levels at the end of the 6 week treatment period	Primary: After six weeks of treatment with ezetimibe, a statistically significant mean reduction was observed in LDL-C (30.5%; P<0.001). Secondary: At six weeks, 674 patients (80.5%) achieved the recommended target LDL-C levels. After six weeks of treatment with ezetimibe, statistically significant mean reductions were observed in TC (20.8%), TG (10.1%), apo B (19.8%), and TC:HDL ratio (19.9%) (P<0.001). There were 50 mild, nonserious adverse events related to ezetimibe reported by 32 patients (3.4%). Frequently reported adverse events included constipation (0.7%), diarrhea (0.4%) and dizziness (0.4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	CAD risk category, on a stable diet and statin regimen for ≥4 weeks before study entry		and the percentage of change in TC, TG, HDL-C, apo B and the TC:HDL-C ratio, safety and tolerability	
Pitsavos et al.[22] (2009) Ezetimibe 10 mg QD All patients were receiving high-dose statin therapy.	OL Patients with HeFH who were receiving treatment with high-dose statins (atorvastatin 80 mg, pravastatin 40 mg, rosuvastatin 40 mg, simvastatin 80 mg, fluvastatin 80 mg)	N=70 12 months	Primary: Lipid and lipoprotein parameters Secondary: Not reported	Primary: After three months, treatment with ezetimibe led to a significant reduction in TC (P<0.05), LDL-C (P<0.05), TG (P<0.05) and apo B (P<0.05), which persisted until 12 months. There were no significant changes in HDL-C, apoA, Lp(a), fibrinogen, or hsCRP with ezetimibe. Secondary: Not reported
Strony et al.[23] (2008) Ezetimibe 10 mg QD coadministered with either pravastatin 10 to 40 mg QD or simvastatin 10 to 80 mg QD	Pooled analysis of 2 ES, MC, OL Patients with primary hypercholesterolemia	N=795 12 to 15 months	Primary: Tolerability Secondary: LDL-C, HDL-C, TG, TC, and proportion of patients achieving LDL-C goal	Primary: Treatment-emergent adverse events were reported in 81% of patients receiving ezetimibe plus pravastatin (15 months) and in 84% of patients receiving ezetimibe plus simvastatin (12 months). The most commonly reported treatment-emergent adverse events were upper respiratory tract infection (18%), headache (11%), musculoskeletal pain (10%), arthralgia (10%), sinusitis (10%), abdominal pain (8%), bronchitis (6%), coughing (6%), nausea (6%), back pain (5%), myalgia (5%), chest pain (5%), and fatigue (5%) with ezetimibe plus pravastatin. The most commonly reported treatment-emergent adverse events were upper respiratory tract infection (19%), arthralgia (11 %), musculoskeletal pain (10%), headache (9%), back pain (8%), myalgia (8%), abdominal pain (7%), nausea (7%), pharyngitis (6%), coughing (5%), fatigue (5%), and urinary tract infection (19%) with ezetimibe plus simvastatin. During the ezetimibe plus pravastatin extension study, 7% experienced serious adverse events. During the ezetimibe plus simvastatin extension

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				study, serious adverse events were reported in 10% of patients. Life-threatening adverse events were reported in four patients in the ezetimibe plus simvastatin study. The incidence of newly reported adverse events did not increase over time in either study. In the ezetimibe plus pravastatin study, 1% of patients experienced increases in ALT/AST >3 X upper limit of normal, whereas this was not reported in the patients receiving ezetimibe plus simvastatin. Secondary: The mean LDL-C was reduced by 36.5 and 40.4% in the ezetimibe plus pravastatin and ezetimibe plus simvastatin studies, respectively. Similar reductions in TC and TG, and an increase in HDL-C, were achieved and maintained throughout the study period in both studies. In the ezetimibe plus pravastatin study, 85% of patients achieved their NCEP ATP III LDL-C goal and 80% of patients in the ezetimibe plus simvastatin study achieved their recommended goal.
Salen et al.[24] (2004) Ezetimibe 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥10 years of age with a diagnosis of sitosterolemia who had plasma sitosterol levels >0.12 mmol/L despite current treatment	N=37 8 weeks	Primary: Percent change from baseline in sitosterol concentration Secondary: Not reported	Primary: Ezetimibe resulted in a mean percent reduction in sitosterol of 21% (P<0.001) compared to a nonsignificant increase of 4% with placebo (P value not reported). The between-group difference in mean percent change in sitosterol was -25% (95% CI, -36.7 to -13.2; P<0.001). The reduction in plasma sitosterol during the DB period was progressive beginning at week two, with greater reduction from baseline observed at each subsequent visit. Secondary: Not reported
Lutjohann et al.[25] (2008) Ezetimibe 10 mg/day	ES Patients ≥10 years of age with a diagnosis of sitosterolemia who had plasma sitosterol levels	N=21 2 years	Primary: Percent change from baseline in sitosterol concentration	Primary: Ezetimibe resulted in significant mean percent reductions in sitosterol (-43.9%; 95% CI, -52.2 to -35.6; P<0.001). Progressively larger reductions in sitosterol were observed during the first 40 weeks of the OL extension phase, with maximal reductions achieved by 52 weeks of treatment (-47.6%; 95% CI, -50.9 to -44.4; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	>0.12 mmol/L despite current treatment		Secondary: Percent change from baseline in campesterol concentration and LDL-C	Secondary: Ezetimibe resulted in significant mean reductions in campesterol (-50.8%; 95% CI, -58.8 to -42.7; P<0.001). Plasma concentrations progressively declined over the first 40 weeks of the trial reaching a maximum reduction of -53.6% (95% CI, -56.9 to -50.3) at week 52. After week 52, plasma concentrations remained generally stable for the remainder of the 104 week treatment period. Ezetimibe resulted in significant mean reductions from baseline in LDL-C (-13.1%; 95% CI, -25.0 to -1.2; P=0.032) at week 104.
Musliner et al.[26] (2008) Ezetimibe 30 mg/day vs placebo All patients continued on OL ezetimibe 10 mg/day for the duration of the trial.	DB, MC, PC, PG, RCT Patients ≥18 years of age with homozygous sitosterolemia who were taking ezetimibe 10 mg/day for ≥6 months prior to enrollment	N=27 26 weeks	Primary: Percent between-group change from baseline in sitosterol Secondary: Between-group changes in campesterol, lathosterol and Achilles tendon thickness size; safety	Primary: Ezetimibe 40 mg/day resulted in a median percent change in sitosterol of 3.3 vs -10.0% with ezetimibe 10 mg/day, resulting in a between-group difference of 9.6% (P=0.180). Secondary: Median percent changes in campesterol were -9.7 vs -0.5% with ezetimibe 10 and 40 mg/day, resulting in a between-group difference of 7.6% (P=0.359). Median percent changes in lathosterol were 0.8 vs 1.1% with ezetimibe 40 and 10 mg/day, resulting in a between-group difference of 5.2% (P=0.701). Achilles tendon thickness increased slightly with ezetimibe 10 mg/day (2.2%) and remained unchanged with 40 mg/day, resulting in a nonsignificant between-group difference of -2.2% (P=0.404). Ezetimibe 40 mg/day was generally well tolerated. Laboratory safety parameters remained stable during the treatment period. No patients receiving ezetimibe in the trial experienced elevations in AST or AST greater than threefold or in creatinine kinase greater than tenfold the upper limit of normal.
Dujovne et al.[27] (2002)	DB, MC, PC, RCT Adult men and women	N=892 12 weeks	Primary: Percent change from baseline to	Primary: The ezetimibe group achieved a mean percent reduction from baseline to end point in the plasma concentration of LDL-C of 16.9% compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD vs placebo	aged ≥18 years with a diagnosis of primary hypercholesterolemia (LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout)		end point in plasma concentration of direct LDL-C Secondary: Changes and percent changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, and HDL-C at end point, changes from baseline HDL_2-C and HDL_3-C, apo AI, apo B, Lp(a) at end point, adverse events	0.4% in the placebo group (P<0.01). Secondary: There was a -17.68% compared to a 1.11% change in the calculated LDL-C from baseline in the ezetimibe and placebo groups, respectively (P<0.01). Ezetimibe also significantly decreased the apo B, TC, and TG as well as significantly increased HDL-C and HDL_3-C from baseline (P<0.01). However, there was no significant change in HDL_2-C and apo AI with ezetimibe compared to placebo (P=0.76 and P=0.50, respectively). Treatment-emergent adverse events occurred in 66% of patients taking ezetimibe and 63% of patients taking placebo. The most commonly reported adverse event in both treatment groups were upper respiratory tract infections and headache. The adverse events were considered to be mild to moderate and were similar between treatment groups.
Knopp et al.[28] (2003) Ezetimibe 10 mg QD vs placebo	DB, MC, PC, RCT Adult men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL)	N=827 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of direct LDL-C Secondary: Changes and percentage changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, HDL-C at end point, HDL_2-C,	Primary: The mean plasma concentration of direct LDL-C from baseline to end point was 17.7% in the ezetimibe group compared to 0.8% in the placebo group (P<0.01). Secondary: Ezetimibe significantly decreased calculated LDL-C, apo B, TC and Lp(a) and significantly increased HDL-C and HDL_2-C (P≤0.01 for all). However, the change in HDL_3-C, apo AI, and TG from baseline did not result in significant differences between treatment groups (P=0.49, P=0.27, P=0.09). The percentage of patients reporting treatment-emergent adverse events was 61% in the ezetimibe group and 65% in the placebo group. No individual adverse event was prevalent in either group and all were considered mild to moderate in severity. Overall, the adverse event profiles were similar between both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			HDL_3-C, apo AI, apo B, Lp(a), adverse events	
Knopp et al.[29] (2003) Ezetimibe 10 mg QD vs placebo	Pooled analysis of 2 DB, MC, PC, RCT Men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout)	N=1,719 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of LDL-C Secondary: Percentage change from baseline in TC, TG, HDL-C, HDL_2-C, HDL_3-C, apo AI, apo B, Lp(a), adverse events	Primary: In the pooled analysis, LDL-C was reduced by a mean 18.2% from baseline in the ezetimibe group compared to an increase of 0.9% in the placebo group (P<0.01). Secondary: Ezetimibe significantly decreased TC, apo B, Lp(a), and TG and increased HDL-C compared to placebo (P<0.01). However, there were no statistically significant differences in the change of HDL_2-C, HDL_3-C and apo AI between ezetimibe and placebo (P=0.08, P=0.06, and P=0.26). The overall adverse event profiles were similar between the ezetimibe and placebo groups. Approximately 62% of patients in the ezetimibe group and 62% of patients in the placebo group reported adverse events. Also, there were no significant between-group differences in the laboratory or clinical safety parameters or gastrointestinal, liver, or muscle side effects.
Wierzbicki et al.[30] (2005) Ezetimibe 10 mg QD vs placebo	PRO Patients with refractory familial hyperlipidemia or intolerance to statin therapy	N=200 Not reported	Primary: LDL-C, TG, HDL-C, CRP, ALT Secondary: Not reported	Primary: Ezetimibe was associated with 7% reductions in LDL-C and 11% reductions in apo B. The proportion of patients achieving LDL-C <3 mmol/L increased from 6 to 18%. There were no significant differences in TG, HDL-C, CRP, or ALT. Secondary: Not reported
Kalogirou et al.[31] (2007) Ezetimibe 10 mg QD vs placebo	PRO Patients with primary dyslipidemia and no evidence of CHD, average 54 years of age, average BMI of 26.9 kg/m^2	N=50 16 weeks	Primary: Lipoprotein subfractions Secondary: Not reported	Primary: A significant median reduction in serum HDL-C concentration from 1.5 mmol/L (1.1 to 2.6) at baseline to 1.4 mmol/L (0.9 to 2.6) posttreatment was observed with ezetimibe treatment. The median change in HDL-C was -6.6% (P<0.001). A significant median reduction in TC from 7.1 mmol/L (4.9 to 11.1) at baseline to 5.8 mmol/L (4.3 to 8.9) posttreatment was observed with ezetimibe treatment. The median change in TC was -15.5% (-34.5 to 4.2%) with ezetimibe

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment (P<0.001 vs placebo). Mean serum TG decreased from 1.5 mmol/L (0.6 to 4.28) at baseline to 1.4 mmol/L (0.6 to 3.2) posttreatment; a median percent change of 9.3% (-32.4 to 15.7%; P<0.05). Mean serum LDL-C levels significantly decreased from 3.8 mmol/L (2.5 to 7.3) at baseline to 3.2 mmol/L (1.8 to 5.4) posttreatment; a median percent change of –20.1% (-51.1 to 23.1%; P<0.001). Secondary: Not reported
Gonzalez-Ortiz et al.[32] (2006) Ezetimibe 10 mg QD vs placebo	DB, PC, RCT Obese, dyslipidemic patients 18 to 45 years old	N=12 90 days	Primary: TC, LDL-C Secondary: HDL-C, TG, VLDL-C	Primary: Ezetimibe-treated patients compared to placebo-treated patients had decreased TC (6.0 vs 4.2 mmol/L; P=0.011) and LDL-C (4.0 vs 2.2 mmol/L; P=0.003) without affecting insulin sensitivity. Secondary: There were no differences in HDL-C, TG, and VLDL-C (P values not significant).
Pearson et al.[33] (2005) Ezetimibe 10 mg QD vs placebo Patients in both groups continued to receive their current dose of statin therapy.	DB, MC, PC, PG Hypercholesterolemic patients ≥18 years of age with LDL-C levels exceeding NCEP ATP III goals while taking a stable, approved dose of any statin, following a cholesterol-lowering diet for ≥6 weeks	N=3,030 6 weeks	Primary: Percent reduction in LDL-C level from baseline after 6 weeks of DB treatment Secondary: Percentage of patients who achieved NCEP ATP III target LDL-C levels in the total population and by NCEP ATP III risk categories	Primary: Ezetimibe added to a statin significantly reduced mean LDL-C levels by an additional 25.8% compared to a reduction of 2.7% with the addition of placebo to statin (95% CI, -24.4 to -21.7%; P<0.001). Secondary: The addition of ezetimibe to statin resulted in an additional 23.8 to 25.7% reduction in LDL-C in all NCEP ATP III risk categories. Treatment differences were -24.0, -19.7, and -19.9% in the CHD or CHD risk equivalent, multiple risk factors, or <2 risk factors groups, respectively (P<0.001 ezetimibe vs placebo for each risk category). No significant differences were found according to age, sex, or race category (P>0.05).
Bays et al.[34] (2006)	DB, MC, PC, PG, RCT	N=86	Primary: Mean percent	Primary: After six weeks of treatment, ezetimibe produced a mean percent decrease

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD vs placebo All patients were receiving colesevelam 3.8 QD.	Men and women with primary hypercholesterolemia	4 to 8 weeks washout period and 6 weeks of treatment	change in LDL-C, mean absolute and mean percent change in HDL-C, non-HDL-C, TC, apo AI and apo B, and median absolute and percent changes in TG and hsCRP from baseline to end of treatment Secondary: Safety and tolerability	in LDL-C of 32.3 vs 21.4% with placebo (P<0.0001). Ezetimibe was significantly more effective placebo at producing mean percent reductions in TC, non-HDL-C, apo B and increases in apo AI (P<0.005 for all). Neither treatment resulted in significant changes in median TG levels compared to baseline (P value not significant). Secondary: Both treatment groups were safe and generally well tolerated.
Blagden et al.[35] (2007) Ezetimibe 10 mg QD vs placebo All patients received atorvastatin 10 mg QD.	DB, MC, PC, RCT Men and women with primary hypercholesterolemia and CHD	N=148 6 weeks	Primary: Mean percentage change in LDL-C from baseline to study end point Secondary: Percentage of patients achieving the new JBS 2 recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L, percentage of patients reaching LDL-C targets, safety and tolerability	Primary: From baseline to week six, ezetimibe and atorvastatin provided significantly greater reductions in adjusted mean LDL-C level compared to atorvastatin monotherapy, (-50.5 vs -36.5%; P<0.0001), equating to an additional 14.1% reduction (95% CI, -17.90 to -10.19). Secondary: A significantly higher proportion of patients on ezetimibe and atorvastatin achieved the new JBS 2 recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L compared to atorvastatin monotherapy (62 vs 12%; P<0.0001 and 93 vs 79%, respectively). Patients receiving ezetimibe and atorvastatin were 12 times more likely to reach LDL-C targets (OR, 12.1; 95% CI, 5.8 to 25.1; P<0.0001) compared to patients receiving atorvastatin monotherapy. Clinical chemistry profiles and the incidence of adverse events were similar in both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rodney et al.[36] (2006) Ezetimibe 10 mg QD vs placebo All patients received simvastatin 20 mg/day.	DB, MC, PC, PG, RCT African-American patients with LDL-C ≥145 mg/dL but ≤250 mg/dL, TG ≤350 mg/dL	N=247 12 weeks	Primary: Mean change from baseline in LDL-C level, total cholesterol, TG, HDL-C, non-HDL-C, apo B Secondary: Not reported	Primary: Patients receiving ezetimibe experienced a statistically significant LDL-C reduction from baseline compared to patients receiving placebo (45.6 vs 28.3%; P≤0.01). Patients receiving ezetimibe experienced a statistically significant reduction in TC from baseline compared to patients receiving placebo (33 vs 21%; P≤0.01). Patients receiving ezetimibe experienced a statistically significant TG reduction from baseline compared patients receiving placebo (22 vs 15%; P≤0.01). Patients receiving ezetimibe experienced a statistically significant non-HDL-C reduction from baseline compared to patients receiving placebo (42 vs 26%; P≤0.01). Patients receiving ezetimibe experienced a statistically significant apo B reduction from baseline compared to patients receiving placebo (38 vs 25%; P≤0.01). There was no difference in the change of HDL-C level from baseline between the two groups (~1-2% increase in each group). There was no statistically significant difference in side effects between the two groups. Secondary: Not reported
Patel et al.[37] (2006) Ezetimibe 10 mg vs placebo	DB, MC, PC, PG, RCT Men and women aged 18 to 75 years with primary hypercholesterolemia (LDL ≥3.3 mmol/L and ≤4.9 mmol/L, TG	N=153 6 weeks	Primary: Mean change in LDL-C level from baseline to 6 weeks, proportion of patients who reached an LDL-C goal of <3 mmol/L	Primary: At six weeks, patients receiving ezetimibe had a mean LDL-C reduction of 14.6% (95% CI, 10.1 to 19.1). At six weeks, a greater number of patients receiving ezetimibe reached an LDL-C goal <3 mmol/L compared to patients receiving placebo (93 vs 75%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received simvastatin.	<3.99 mmol/L) and documented CHD ≥3 months prior to baseline who were not receiving pharmacologic lipid management therapy		at end point Secondary: Changes in serum TC, TG and HDL-C levels, safety and tolerability	Secondary: At six weeks, there was a significant additional reduction in TC of 0.69 mmol/L in patients receiving ezetimibe compared to patients receiving placebo (95% CI, 0.48 to 0.90; P<0.0001). There was a 20.4% reduction in TG levels in the ezetimibe group compared to a 12.4% reduction in the placebo group (P=0.06). Baseline HDL-C levels increased by 6% in both treatment groups. In the ezetimibe group, 40% of patients had at least one treatment-emergent adverse event compared to 25% in the placebo group. The overall incidence of adverse events were not significant among the two groups (P=0.07). Two patients in the ezetimibe group and one patient in the placebo group experienced a serious adverse event unrelated to the study medications.
Landry et al.[38] (2006) Ezetimibe 10 mg QD vs placebo All patients received simvastatin.	MC, PC, RCT Men and women ≥18 years of age, patients on predialysis with creatinine level ≥1.7 mg/dL, hemodialysis, or peritoneal dialysis	N=203 6 months	Primary: LDL-C, TC, non-HDL-C, HDL-C, TG, apo B, apo AI Secondary: Tolerability and safety	Primary: Both groups had statistically reduced LDL-C at one, three, and six months compared to baseline (P<0.0001). The addition of ezetimibe to simvastatin was associated with 27, 26, and 21% reductions in LDL-C at one, three, and six months, respectively. The addition of ezetimibe to simvastatin was associated with 16, 16, and 14% reductions in TC at one, three, and six months, respectively. The addition of ezetimibe to simvastatin was associated with 24, 25, and 19% reductions in non-HDL-C at one, three, and six months, respectively. The addition of ezetimibe to simvastatin was associated with 15, 14, and 12% reductions in apo B at one, three, and six months, respectively. There were no significant effects in HDL-C, TG, or apo AI (P value not significant) except for 7% increase of HDL-C at three months (P=0.02). Secondary: There were no significant differences in muscle pain, muscle weakness, abdominal discomfort, nausea, constipation, or appetite loss between groups (P value not significant). More patients on ezetimibe reported diarrhea (27 vs 12%; P=0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences in CK levels or abnormal hepatic transaminase levels.
Bays et al.[39] (2008) Ezetimibe 10 mg QD vs placebo All patients received simvastatin 80 mg QD.	ES Patients ≥18 years of age with primary hypercholesterolemia	N=768 48 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: In general, combination therapy did not substantively differ from simvastatin with respect to total adverse events (73 vs 69%), treatment related adverse events (13.5 vs 11.4%), treatment related serious adverse events (1 vs 0%), discontinuations due to treatment related adverse events (2.8 vs 2.6%) or discontinuations due to treatment-related serious adverse events (1 vs 0%). Combination therapy had a slightly higher rate of serious adverse events (5.2 vs 2.6%) and discontinuations due to adverse events (4.5 vs 2.6%) compared to simvastatin (P>0.20). Based on investigator assessment of causality, rates were similar between the treatments. There are no remarkable observations of between-treatment group differences whether or not they are related to a specific tissue or body system. In general, combination therapy did not differ from simvastatin with respect to total laboratory adverse events (12 vs 12%), treatment related laboratory adverse events (6.2 vs 5.3%), total laboratory serious adverse events (0 vs 0%), treatment related laboratory serious adverse events (0 vs 0%) or discontinuations due to laboratory serious adverse events (0 vs 0%). Secondary: Not reported
van der Graaf et al.[40] (2008) Ezetimibe 10 mg QD vs	DB, MC, PC, RCT Patients 10 to 17 years of age with heFH	N=248 53 weeks	Primary: Percent change from baseline in LDL-C after six weeks Secondary: TC, HDL-C, TG,	Primary: After six weeks of therapy, ezetimibe lowered LDL-C by -49.5% compared to -34.4% with placebo (P<0.01). Secondary: After six weeks of therapy, ezetimibe was more effective compared to placebo in lowering TC (-38.2 vs 26.3%; P<0.01), non-HDL-C (-46.8 vs -32.7%; P<0.01), and apo B (-38.9 vs -26.7%; P<0.01). There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo All patients received simvastatin 10 to 40 mg QD			non-HDL-C, apo B after six weeks, 33 weeks and 53 weeks, percentage of patients achieving LDL-C goals	significant difference in HDL-C (P<0.95) or TG (P<0.48) among the treatment groups. After 33 weeks of therapy, ezetimibe was more effective compared to placebo in lowering LDL-C (-54 vs 38.1%; P<0.01), TC (-42.5 vs 29.3%; P<0.01), non-HDL-C (-51.3 vs -35.7%; P<0.01), TG (-20 vs -13.4%; P<0.01) and apo B (-42.6 vs -27.9%; P<0.01). There was no significant difference in HDL-C (P=0.58) among the treatment groups. The percentage of patients achieving the American Academy of Pediatrics acceptable LDL-C goal of <130 mg/dL and ideal LDL-C goal of <110 mg/dL was significantly higher with ezetimibe (77 and 63%, respectively) compared to placebo (53 and 27%, respectively; P<0.01) in patients receiving simvastatin 40 mg/day. After 53 weeks of therapy, the mean percent change in LDL-C in the overall population was -49.1% from baseline. Mean percent changes were -38.5% in TC, -46.4% in non-HDL-C, and median percent changes of -16.6% were observed in TG. The HDL-C levels were 3.3% above baseline levels at trial end.
Masana et al.[41] (2005) Ezetimibe 10 mg QD vs placebo All patients received simvastatin 10 mg/day, titrated up to 80 mg/day.	DB, ES, MC, RCT Patients with primary hypercholesterolemia ≥18 years of age, currently taking a stable daily dose of a statin ≥6 weeks, with LDL-C above the NCEP ATP II guideline target level, TG <350 mg/dL	N=355 48 weeks	Primary: Percent change from baseline in LDL-C between the study groups at week 12 Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, non-HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C at 12 weeks	Primary: At week 12, patients receiving ezetimibe experienced a statistically significant 27% reduction in LDL-C compared to patients receiving placebo (P<0.001). The benefit was maintained up to week 48 of the study. Secondary: At week 12, patients receiving ezetimibe experienced a statistically significant reduction in total cholesterol, TG, non-HDL-C, ratios of LDL-C:HDL-C, and TC:HDL-C, compared to patients receiving placebo (P<0.001). At week 12, patients receiving ezetimibe experienced a non-significant 2.6% increase in HDL-C compared to patients receiving placebo (P=0.07). Treatment-related adverse effects were similar between the two treatments (17 and 19%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no cases of rhabdomyolysis or myopathy during the study.
Gagné et al.[42] (2002) Ezetimibe 10 mg QD vs placebo All patients were receiving statin therapy.	DB, MC, PC, RCT Adults aged ≥18 years, currently on a stable daily dose of a statin for ≥6 weeks, must have been previously instructed on a cholesterol-lowering diet, LDL-C at or above recommended target level for patient's risk category (<160 mg/dL for patients without CHD and ≤1 risk factor, <130 mg/dL for patients without CHD and ≥2 risk factors, ≤100 mg/dL for patients with established but stable CHD or CHD-equivalent disease)	N=769 8 weeks	Primary: Mean percentage change in LDL-C from baseline to end point Secondary: Percentage of patients who achieved NCEP ATP II target levels for LDL-C, HDL-C, TC, TG, adverse events	Primary: There was an additional LDL-C reduction of 25.1% in patients receiving ezetimibe therapy compared to a reduction of 3.7% in patients receiving placebo (P<0.001 for between-group differences). Secondary: Including patients who were technically at LDL-C goal at baseline, 75.5% of patients taking ezetimibe plus statin achieved the prespecified NCEP ATP II target LDL-C levels at end point compared to 27.3% of patients taking placebo plus statin (OR, 19.6; P<0.001). For those patients who were not at target LDL-C levels at baseline, 71.5 vs 18.9% of patients taking ezetimibe and placebo, respectively, achieved target LDL-C goals. HDL-C was increased by 2.7% compared to an increase of 1.0% in patients taking ezetimibe and placebo, respectively (P<0.05). TG decreased by 14.0 and 2.9%, respectively (P<0.001). TC was also improved significantly with coadministration of ezetimibe compared to placebo (P<0.001). The overall incidence of treatment-related adverse events was similar between both groups (21 vs 17%).
Denke et al.[43] (2006) Ezetimibe 10 mg QD vs placebo All patients were	DB, MC, PC, PG, RCT Men and women ≥18 years of age with diabetes, metabolic syndrome without diabetes, or neither disorder who had LDL-C levels exceeding the NCEP ATP III goals who	N=3,030 6 weeks	Primary: LDL-C reduction and additional lipid parameters, safety and tolerability Secondary: Not reported	Primary: After six weeks of treatment, the addition of ezetimibe to ongoing statin therapy reduced LDL-C levels in patients with diabetes by 28%, metabolic syndrome by 24%, or elevated LDL-C levels without diabetes or the metabolic syndrome by 26%, compared to a 3% reduction in the placebo group (P<0.001 for all). TG and HDL-C levels were significantly reduced in patients with diabetes and metabolic syndrome when ezetimibe was added to statin therapy compared to placebo (P<0.002). Non-HDL levels, TC, apo B:apo AI ratio, and CRP levels improved significantly in patients with diabetes and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
receiving statin therapy.	were taking a stable, approved dose of any statin, had been following a cholesterol -lowering diet for ≥6 weeks prior to study entry with TG levels ≤350 mg/dL			patients with elevated LDL-C levels without diabetes or metabolic syndrome when ezetimibe was added to statin therapy compared to placebo. Drug-related adverse events occurred in 5.2% in the placebo group and 5.1% in the ezetimibe group. Drug-related adverse events that led to drug discontinuation occurred in 1.6% in the placebo group and 0.9% in the ezetimibe group. There were no significant differences between the two groups in elevation of ALT, AST or in muscle CK beyond predefined limits. Secondary: Not reported
Pearson et al.[44] (2006) Ezetimibe 10 mg QD vs placebo All patients were receiving statin therapy.	DB, MC, PG, PC, RCT Men and women ≥18 years of age including white, African American, Hispanic or other who followed a cholesterol-lowering diet, were taking a stable approved dose of any US marketed statin for ≥6 weeks before study entry, with LDL-C levels greater than the NCEP ATP III goal	N=3,030 6 weeks	Primary: LDL-C and additional parameters and percentage of patients reaching LDL goal for the NCEP ATP III in racial and ethnic subgroups Secondary: Safety and tolerability	Primary: The addition of ezetimibe to ongoing statin therapy significantly reduced LDL-C, TC, non-HDL and HDL-C levels compared to placebo (P<0.001). This effect was consistent across race and ethnicity (P>0.50 for treatment-by-race interactions). CRP level reduction was statistically significant in patients receiving ezetimibe compared to placebo (P<0.001). The treatment-by-race interaction was not statistically significant (P=0.83), indicating a consistent treatment effect of lowering CRP levels across race and ethnicity groups. Ezetimibe added to statin therapy significantly increased the percentage of patients attaining their LDL-C goal for the NCEP ATP III in African Americans by 63%, Hispanics by 64.8% and whites by 72.3%, compared to placebo (P<0.001). Secondary: The addition of ezetimibe to ongoing statin therapy was well tolerated with an overall safety profile similar in all patient groups by race or ethnicity.
Pearson et al.[45] (2005) EASE	DB, MC, PG, RCT Subanalysis of the	N=3,030 6 weeks	Primary: Mean change from baseline in LDL-C	Primary: Compared to placebo, patients receiving ezetimibe experienced an LDL-C reduction of 23% (white patients), 23% (African American patients), and

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Ezetimibe 10 mg QD vs placebo All patients were receiving statin therapy.	EASE study; patients >65 years old with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals, on an approved dose of a statin for 6 weeks prior to study entry, following a cholesterol-lowering diet		level, proportion of patients who reached LDL-C target across different races and ethnicities, change in serum cholesterol, TG, HDL at 6 weeks Secondary: Not reported	21% (Hispanic patients) from baseline (P<0.001). The difference in LDL-C lowering among the three races studied was not statistically significant (P>0.5). A significantly greater proportion of patients randomized to ezetimibe achieved their NCEP ATP LDL-C goal compared to placebo (P<0.001). Patients receiving ezetimibe experienced a TC reduction of 15.3 mg/dL from baseline compared to patients receiving placebo (P<0.001). Patients receiving ezetimibe experienced a TG reduction of 11.5 mg/dL from baseline compared patients receiving placebo (P<0.001). Patients receiving ezetimibe experienced an increase in HDL-C of 2.1 mg/dL from baseline compared to patients receiving placebo (P<0.001). Side effects were similar across treatment groups and races. Secondary: Not reported
Mikhailidis et al.[46] (2007) Ezetimibe 10 mg QD vs placebo All patients were receiving statin therapy.	MA (21 trials) Adults ≥18 years with diagnoses of nonfamilial or familial hypercholesterolemia, hyperlipidemia, and homozygous familial sitosterolemia; with LDL-C levels above NCEP ATP II/III guideline criteria	N=5,039 6 to 48 weeks	Primary: Total number of patients attaining LDL-C goal; changes in TC, LDL-C, and HDL-C from baseline to end point Secondary: Not reported	Primary: The analysis of five RCTs indicated that when compared to placebo in combination with a statin, the RR of obtaining the LDL-C treatment goal was higher for patients in the ezetimibe and statin groups (P<0.0001). A WMD between treatments significantly favored the ezetimibe and statin combination therapy over placebo and statin: for TC, a WMD of -16.1% (CI, -17.3 to -14.8); for LDL-C, a WMD of -23.6% (CI, -25.6 to -21.7); and for HDL-C, a WMD of 1.7% (CI, 0.9 to 2.5) (P<0.0001 for all). In an analysis of patients with or without CHD (in addition to hypercholesterolemia), the ezetimibe and statin combination was favored over placebo and statin for the following WMD: LDL-C -23.6% (P<0.0001); TC -16.1% (P<0.0001); HDL-C 1.7% (P<0.0001); TG -10.7%; apo B -17.3%; RR, LDL-C treatment goal 3.4% (P<0.0001). The difference between treatments in all studies favored the ezetimibe and

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				statin combination therapy for all outcomes except TG and HDL-C. An analysis of data from a 48-week ES correlated with the pooled estimates of the short-term studies in the MA. This data showed that the ezetimibe and simvastatin combination resulted in significantly lower levels of LDL-C, TC, and TG when compared to the placebo and simvastatin combination (reductions of 20.4, 13.4 and 13.6%, respectively; P<0.001 for the difference between treatments). Secondary: Not reported
Pearson et al.[47] (2009) <u>Group 1</u> Ezetimibe 10 mg QD vs placebo and <u>Group 2</u> Ezetimibe 10 mg QD vs placebo All patients in Group 2 were receiving statin therapy.	MA (11 trials) Patients with hypercholesterolemia and hsCRP ≤10 mg/L	N=5,271 (11 trials) 6 to 12 weeks	Primary: Mean change in hsCRP and LDL-C Secondary: Not reported	Primary: Treatment with ezetimibe monotherapy led to a mean 1% reduction in CRP compared to a mean 5% increase with placebo after 12 weeks (P=0.09). Treatment with ezetimibe and statin combination therapy led to a mean 12% decrease in CRP compared to a mean 1% decrease with statin monotherapy after six to eight weeks (P<0.001). Treatment with ezetimibe monotherapy led to a mean 18% reduction in LDL-C compared to a mean 0.5% increase with placebo after 12 weeks of therapy (P<0.001). Treatment with ezetimibe and statin combination therapy led to a mean 27% decrease in LDL-C compared to a mean 3% decrease with statin monotherapy after six to eight weeks (P<0.001). Secondary: Not reported
Farnier et al.[48] (2005)	DB, MC, PC, RCT	N=619	Primary: Percent change in	Primary: The mean percent change in LDL-C reduction was significantly greater in

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Ezetimibe 10 mg and fenofibrate 160 mg QD vs ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs placebo	Men and women 18 to 75 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or 10-year CHD risk >20%	12 weeks	LDL-C from baseline to study end point Secondary: Percent change in other lipid, non-lipid, and lipoprotein parameters from baseline to study end point	the micronized fenofibrate and ezetimibe group when compared to the other treatment groups (P<0.001 compared to micronized fenofibrate and ezetimibe). These reductions were 13.4% in the ezetimibe group, 5.5% in the micronized fenofibrate group, and 20.4% in the micronized fenofibrate and ezetimibe group. Secondary: When compared to micronized fenofibrate or ezetimibe monotherapy, significant reductions in apo B, non-HDL-C and LDL-C were observed in the micronized fenofibrate and ezetimibe group; P<0.001. When compared to placebo, significant decreases in TG levels and significant increases in HDL-C level were observed in both the micronized fenofibrate plus ezetimibe and micronized fenofibrate treatment groups; P<0.001. The percent changes from baseline to study end point were as follows: -11.8% in TC, 3.9% in HDL-C, -11.1% in TG, and -6.1% in high sensitivity CRP in the ezetimibe group; -10.8% in TC, 18.8% in HDL-C, -43.2% in TG, and -28.0% in hsCRP in the micronized fenofibrate group; -22.4% in TC, 19.0% in HDL-C, -44.0% in TG, and -27.3% in hsCRP in the micronized fenofibrate and ezetimibe group (P<0.05 for all).
Tribble et al.[49] (2008) Ezetimibe 10 mg and fenofibrate 160 mg QD (FENO + EZE) vs ezetimibe 10 mg QD (EZE) vs fenofibrate 160 mg QD (FENO)	DB, MC, PC, RCT Patients 18 to 75 years of age with mixed hyperlipidemia (LDL-C 130 to 220 mg/dL and TG 200 to 500 mg/dL) and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=625 12 weeks	Primary: Changes in cholesterol mass within the major lipoprotein fractions and subfractions and LDL particle distribution profiles and particle size Secondary: Not reported	Primary: The effects of EZE, FENO, and FENO + EZE on VLDL subfractions were similar to those for VLDL overall. All active treatments reduced IDL-C. Treatment with FENO significantly reduced LDL-C1, LDL-C3, and LDL-C4 and significantly increased LDL-C2 compared to placebo. FENO + EZE produced a pattern of changes similar to those of FENO alone. The reductions in LDL-C1 and LDL-C3 were greater with the combination due to the added effects of EZE. There were no significant changes in cholesterol associated with Lp(a). Fenofibrate and FENO + EZE increased median HDL-C2 and HDL-C3 compared to EZE and placebo. In patients treated with EZE, there were reductions in VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL density distributions or

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vs placebo				changes in the HDL-C range. In patients treated with FENO, there were reductions in VLDL-C and IDL-C. HDL-C was increased and there was a shift in the distribution of LDL toward larger, more buoyant LDL particles with a small effect on LDL-C values overall. In patients treated with FENO + EZE, there were reductions in VLDL-C, IDL-C, and LDL-C. HDL-C was increased and there was a shift from smaller, more dense to larger, more buoyant LDL subfractions. EZE did not significantly affect LDL peak particle size. FENO and FENO + EZE increased LDL peak particle size. Secondary: Not reported
McKenney et al.[50] (2006) Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs ezetimibe 10 mg QD for 12 weeks, then fenofibrate 160 mg and ezetimibe 10 mg QD for 48 weeks	DB Patient who completed base study with mixed hyperlipidemia	N=576 48 weeks	Primary: Percent change in LDL-C from baseline of the base study to study end point in the extension Secondary: Percent change from baseline to study end point in TC, HDL-C, TG, non-HDL-C, apo B, apo AI, and hsCRP	Primary: Fenofibrate plus ezetimibe showed significantly greater percent reductions in LDL-C compared to fenofibrate alone (-22.0 vs -8.6; P<0.001). Secondary: Fenofibrate plus ezetimibe showed significantly greater percent reductions from baseline to extension study end point in TC (-23.2 vs -13.6; P<0.001), TG (-46.0 vs -41.0; P=0.002), non-HDL-C (-31.6 vs -19.4; P<0.001), and apo B (-25.2 vs -16.2; P<0.001) compared to fenofibrate. There was a significantly greater percent increase in HDL-C (20.9 vs 17.8; P=0.02) with fenofibrate plus ezetimibe vs fenofibrate alone. There was not a significantly greater percent increase in apo AI (10.1 vs 7.8; P=0.12) with fenofibrate plus ezetimibe vs fenofibrate alone. Reductions in median hsCRP levels were not different between treatments (-25.3 vs -21.1; P=0.46) for fenofibrate plus ezetimibe vs fenofibrate alone, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 12 weeks, then fenofibrate 160 mg for 48 weeks				
Ballantyne et al.[51] (2003) Ezetimibe 10 mg QD and atorvastatin 10 to 80 mg QD vs ezetimibe 10 mg QD vs atorvastatin 10 to 80 mg QD vs placebo	DB, PC, RCT Men and women aged ≥18 years with primary hypercholesterolemia (LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL)	N=628 12 weeks	Primary: Percentage reduction in direct LDL-C from baseline to final assessment Secondary: Change from baseline to final assessment for calculated LDL-C, TC, TG, HDL-C, TC:HDL-C ratio, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, Lp(a), direct LDL-C:HDL-C ratio, adverse events	Primary: There was a significantly greater mean reduction of direct LDL-C from baseline to final assessment in the ezetimibe plus atorvastatin group compared to either atorvastatin alone (P<0.01) or ezetimibe alone (P<0.01). Mean changes in direct LDL-C ranged from -50 to -60% in the combination group compared to -35 to -51% in the atorvastatin alone group (P<0.01). Secondary: Calculated LDL-C was also significantly reduced more commonly in the combination group than all doses of atorvastatin monotherapy (P<0.01). Greater reductions in LDL-C, TC, and TG were observed with increasing doses of atorvastatin monotherapy. However, there was not a favorable dose response with HDL-C. There were similar reductions in LDL-C (50 vs 51%), TC:HDL-C ratio (43 vs 41%), and TG (both 31%) with coadministration of ezetimibe plus atorvastatin 10 mg and the maximal dose of atorvastatin monotherapy, respectively. However, there was a significantly greater increase in HDL-C (9 vs 3%) with the combination group. Reductions in apo B, non–HDL-C, and direct LDL-C:HDL-C ratio from baseline were significantly greater in the combination group compared to both atorvastatin monotherapy (P<0.01 for all) and ezetimibe monotherapy (P<0.01 for all). However, increases in HDL_2-C (P=0.53), HDL_3-C (P=0.06), apo AI (P=0.31), and Lp(a) (P=0.50) did not significantly differ between the combination therapy and atorvastatin monotherapy groups. There also was no significant difference between the combination therapy and ezetimibe

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				monotherapy groups for increases in these same parameters: HDL_2-C (P=0.08), HDL_3-C (P=0.67), apo AI (P=0.80), and Lp(a) (P=0.92). The combination of ezetimibe plus atorvastatin was well-tolerated. Treatment-emergent adverse events were reported in 17% of patients receiving atorvastatin monotherapy and 23% of patients receiving combination therapy. The majority of adverse events were mild to moderate in severity.
Kerzner et al.[52] (2003) Ezetimibe 10 mg QD and lovastatin 10 to 40 mg QD vs ezetimibe 10 mg QD vs lovastatin 10 to 40 mg QD vs placebo	DB, MC, PC, RCT Men and women aged ≥18 years with mean plasma LDL-C 145 to 250 mg/dL as calculated by Friedewald equation, mean TG ≤350 mg/dL	N=548 12 weeks	Primary: Percentage decrease in directly measured LDL-C from baseline to study end point Secondary: Change from baseline to end point for calculated LDL-C, TC, TG, HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, apo AI, direct LDL-C:HDL-C ratio, adverse events	Primary: The reduction in plasma levels of direct LDL-C from baseline to end point was significantly greater in the combination group of ezetimibe plus lovastatin compared to either lovastatin or ezetimibe monotherapy (P<0.01 for both). The mean percentage decrease in direct LDL-C in the combination group was significantly greater than the decrease obtained from the corresponding lovastatin dose or next higher dose of lovastatin monotherapy (P<0.01). The mean percentage change in LDL-C achieved with combination ezetimibe plus lovastatin 10 mg was similar to the highest lovastatin dose of 40 mg monotherapy (P=0.10). Secondary: In comparison to lovastatin monotherapy, the combination group significantly improved calculated LDL-C, TC, TG, HDL-C, apo B, non–HDL-C, HDL_2-C, HDL_3-C, direct LDL-C:HDL-C ratio (P<0.01 for all), and apo AI (P=0.04). The combination of ezetimibe plus lovastatin significantly increased HDL-C at lovastatin doses of 20 and 40 mg compared to the same lovastatin monotherapy dose (P<0.01 and P<0.02, respectively) and significantly decreased TG levels (P<0.01 for both). Treatment-related adverse events were reported for 16% of patients receiving lovastatin monotherapy and 17% of patients receiving combination therapy. The safety profile for the combination group was similar to that for the lovastatin monotherapy and placebo group.
Melani et al.[53]	DB, MC, PC, RCT	N=538	Primary:	Primary:

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(2003) Ezetimibe 10 mg QD and pravastatin 10 to 40 mg QD vs ezetimibe 10 mg QD vs pravastatin 10 to 40 mg QD vs placebo	Men and women 20 to 86 years old with primary hypercholesterolemia (LDL-C 150 to 250 mg/dL and TG ≤350 mg/dL)	12 weeks	Percent change in direct LDL-C from baseline to study end point Secondary: Mean change and percent change from baseline in LDL-C as calculated by the Friedewald equation, TC, TG, HDL-C, direct LDL-C:HDL-C and TC:HDL-C ratio, non–HDL-C, apo AI, apo B, HDL_2-C, HDL_3-C, Lp(a)	A mean percent change of –38% for the combination therapy and -24% for pravastatin monotherapy was observed. The combination therapy was significantly more effective at reducing plasma levels of direct LDL-C from baseline to end point (P<0.01). The combination group had a mean percentage change in direct LDL-C ranging from -34 to -41% compared to -20 to –29% for individual doses of pravastatin monotherapy. When the combination therapy was compared to its corresponding pravastatin dose, the incremental mean percentage reductions in direct LDL-C were statistically significant in favor of the combination therapy (P≤0.01). In addition, the coadministration of ezetimibe plus pravastatin 10 mg produced a larger mean percentage reduction in direct LDL-C compared to the highest dose of pravastatin monotherapy (P≤0.05). Secondary: In comparison to pravastatin monotherapy, the combination therapy improved calculated LDL-C, TG, TC, apo B, non–HDL-C, direct LDL-C:HDL-C, and TC:HDL-C (P<0.01 for all). Both direct and calculated LDL-C levels at all pravastatin doses were significantly reduced in the combination group (P<0.01). TG was also significantly reduced in the combination group at pravastatin doses of 10 and 20 mg compared to pravastatin monotherapy (P<0.05). Although the combination therapy produced greater increases in HDL-C at the 10 and 40 mg doses, it was not significant. The differences in change in HDL_2-C, HDL_3-C, apo AI, and Lp(a) between the combination group and pravastatin monotherapy were determined to be not significant. Coadministration of ezetimibe and pravastatin was well tolerated and the overall safety profile was similar to pravastatin monotherapy and placebo. There was no evidence to suggest that combination therapy would increase the risk of developing any non-laboratory adverse event.
Hong et al.[54] (2018) I-ROSETTE	DB, MC, RCT Patients 19 to 79 years of age with	N=389 8 weeks	Primary: Change from baseline in LDL-C between the	Primary: The percent changes in adjusted mean LDL-C level at eight weeks compared with baseline values were –57.0% and –44.4% in the total ezetimibe/rosuvastatin and total rosuvastatin groups, respectively.

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Ezetimibe 10 mg/rosuvastatin 20 mg vs ezetimibe 10 mg/rosuvastatin 10 mg vs ezetimibe 10 mg/rosuvastatin 5 mg vs rosuvastatin 20 mg vs rosuvastatin 10 mg vs rosuvastatin 5 mg	hypercholesterolemia requiring medical treatment		ezetimibe/rosuvastatin and rosuvastatin treatment groups Secondary: Adverse events	Treatment with ezetimibe/rosuvastatin resulted in a greater lipid-lowering effect compared with treatment with rosuvastatin alone (differences, –12.6 mg/dL; 95% CI, –16.5 to –8.6; P<0.001). Secondary: The most common adverse events were gastrointestinal disorders, followed by investigations and musculoskeletal and connective tissue disorders. There were no significant differences in the overall incidence of adverse events, adverse drug reactions, or serious adverse events. Laboratory findings, including liver function test results and creatinine kinase levels, were comparable between groups.
Ose et al.[55] (2007) Simvastatin 10, 20, 40, or 80 mg/day vs ezetimibe-simvastatin 10-10,	DB, ES, MC, RCT Patients 22 to 83 years, with primary hyper-cholesterolemia (LDL-C between 145 and 250 mg/dL and TG <350 mg/dL) who were randomized to ezetimibe-simvastatin	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG, TC, non-HDL, CRP, LDL-C:HDL-C ratio, TC:HDL-C ratio, proportion of patients reaching LDL-C target	Primary: Across all doses, patients receiving ezetimibe-simvastatin experienced a statistically significant LDL-C reduction from baseline compared to the simvastatin monotherapy group (53.7 vs 38.8%; P<0.001). Across all doses, patients receiving ezetimibe-simvastatin combination therapy experienced a statistically significant reduction from baseline in TG, TC, non-HDL, CRP, LDL-C:HDL-C ratio, and TC:HDL-C ratio compared to the simvastatin monotherapy group (P<0.001).

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10-20, 10-40, and 10-80 mg/day vs ezetimibe 10 mg QD vs placebo	10-10, 10-20, 10-40, or 10-80 mg combination tablet, simvastatin 10, 20, 40, or 80 mg monotherapy, ezetimibe 10 mg, or placebo		(<100 or <70 mg/dL) Secondary: Not reported	Significantly greater proportion of patients randomized to the ezetimibe-simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (79.2 vs 47.9%; P<0.001). A greater proportion of patients randomized to the ezetimibe-simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (30.4 vs 7%; P<0.001). The incidence of drug-related adverse effects was similar in the ezetimibe-simvastatin and simvastatin monotherapy groups (7.4 vs 5.5%, respectively). Secondary: Not reported
Goldberg et al.[56] (2004) Ezetimibe 10 mg/day and simvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, ALT and AST ≤2 times the upper limit of normal, no active liver disease, CK ≤1.5 times the upper limit of normal	N=887 20 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP; proportion of patients reaching their NCEP ATP III LDL-C goal <130 or <100 mg/dL at 12 weeks	Primary: Averaged across all doses, combination therapy was associated with a significant 14.8% reduction in LDL-C at 12 weeks compared to simvastatin (53.2 vs 38.5%; P<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (P<0.001). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130 or <100 mg/dL at 12 weeks compared to simvastatin (92 and 82% vs 82 and 43%, respectively; P<0.001). Averaged across all doses, combination therapy was not associated with a

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				significant change in HDL-C compared to simvastatin (P=0.53). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups, but were more frequent than with ezetimibe and placebo (13, 14, 9 and 9%, respectively; P values not reported).
Davidson et al.[57] (2002) Ezetimibe 10 mg/day plus simvastatin 10, 20, 40, or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients >18 years of age with primary hypercholesterolemia	N=668 20 week	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (49.9 vs 36.1%; P<0.001). Similar results were observed with combination therapy compared to ezetimibe (49.9 vs 18.1%; P<0.001). Combination therapy (simvastatin 10 mg) and simvastatin 80 mg produced a 44% reduction in LDL-C at 12 weeks (P value not reported). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks, compared to the next highest dose of simvastatin (P<0.01). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C and apo B at 12 weeks compared to simvastatin (P<0.01 for all). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to simvastatin (P=0.03). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non–HDL-C and apo B at 12 weeks compared to ezetimibe (P<0.01 for all). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to ezetimibe (P=0.02). A significantly greater proportion of patients receiving combination

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				therapy experienced a reduction in LDL-C >50% from baseline compared to simvastatin (P value not reported). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups (72 vs 69%, respectively; P value not reported).
Bays et al.[58] (2004) Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients 18 to 80 years of age with primary hypercholesterolemia with LDL-C >145 but ≤150 mg/dL and TG ≤350 mg/dL	N=1,528 24 weeks	Primary: Percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP; proportion of patients reaching their NCEP ATP III LDL-C goal of <130, <100 or <70 mg/dL at 12 weeks	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (53 vs 39%; P<0.001) and ezetimibe (53 vs 18.9%; P<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (P<0.001). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130, <100 or <70 mg/dL at 12 weeks compared to simvastatin (92.2, 78.6 and 38.7 vs 79.2, 45.9 and 7.0%, respectively; P<0.001 for al). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (P=0.607). Treatment-related adverse effects were similar in the pooled simvastatin, combination and ezetimibe groups, but were more frequent than placebo (14.8, 15.1, 12.8 and 8.1%, respectively; P values not reported).
Rosen et al.[59] (2013)	AC, DB, MC, RCT Patients ≥18 and <80	N=808 12 weeks (6	Primary: Percent change from baseline in	Primary: Treatment with EZ/S 10/20 mg resulted in a significantly greater reduction in LDL-C compared with doubling the baseline statin dose (−23.13 vs

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Ezetimibe/ simvastatin (EZ/S) 10/20 mg vs doubling the run-in statin dose (to simvastatin 40 mg or atorvastatin 20 mg) vs switching to rosuvastatin 10 mg	years old with type 1 or 2 diabetes mellitus ($HbA_{1c} \leq 8.5\%$) and symptomatic CVD, who were naïve to statin and/or ezetimibe or were taking a stable dose of approved lipid-lowering therapy	weeks of DB treatment after run-in period)	LDL-C at week 6 Secondary: Percent change from baseline in TC, TG, HDL-C, non-HDL-C, Apo B, Apo A-I, and high-sensitivity C-reactive protein (hsCRP) at week 6 and the percent of patients with LDL-C <70 mg/dL at week 6, safety	−8.37%; P< 0.001). In the population of patients receiving simvastatin 20 mg or atorvastatin 10 mg at baseline, the percent reduction in LDL-C was numerically greater when switched to EZ/S than when switched to rosuvastatin 10 mg following six weeks of treatment (−23.13 vs −19.32%; P=0.060). Secondary: There were significantly greater reductions in TC, Apo B, and non-HDL-C in subjects taking EZ/S 10/20 mg compared with subjects who doubled their statin dose and with those taking rosuvastatin 10 mg. For all other lipids and lipoproteins, the percent changes were not statistically significantly different between treatments. The percent of patients reaching LDL-C goal of <70 mg/dL was significantly greater with ezetimibe/simvastatin (54.5%) vs doubling the baseline statin dose (27.0%) or switching to rosuvastatin 10 mg (42.5%). The safety profile appeared generally comparable between all groups.
Foody et al.[60] (2013) Add-on group (patients who were initially on simvastatin, atorvastatin, or rosuvastatin monotherapy and added ezetimibe onto this therapy) vs titrator group (patients who either titrated their initial statin dose	OS, RETRO Patients ≥18 years of age with a diagnosis of CHD or CHD risk-equivalent who had a prescription for statin monotherapy with baseline and follow-up LDL-C values, as well as no overlap with other lipid-lowering therapy and who had no discontinuations of lipid-lowering therapy at baseline or follow-up during the study period	N=15,365 Minimum of 6 weeks	Primary: Mean percent change from baseline in LDL-C and percentage of patients attaining LDL-C goals <70 mg/dL and <100 mg/dL Secondary: Not reported	Primary: The mean LDL-C levels at baseline were significantly higher in the add-on groups for each statin compared with those of the titrators. At follow-up, LDL-C levels were reduced more in the add-on groups (80 to 85 mg/dL) than in the titrator groups (87 to 95 mg/dL). Both the absolute changes in LDL-C levels and the percent changes from baseline were significantly greater in the add-on groups than in the titrator groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or switched to higher-potency statin monotherapy)				
Feldman et al.[61] (2006) Ezetimibe-simvastatin 10-10, 10-20, 10-40, or 10-80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	MA (3 DB, PC, RCTs) Patients with primary hypercholesterolemia	N=3,083 28 weeks	Primary: Percent change from baseline in LDL-C, TG, non-HDL-C, apo B and hsCRP; achievement of LDL-C <100 mg/dL at week-12 among patients <65 and ≥65 years of age Secondary: Not reported	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C, TG, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (*P*<0.001 for all). These affects did not differ between the older and younger patients (*P* value not reported). Combination therapy and simvastatin produced comparable increases in HDL-C (8 vs 7%, respectively; *P* value not reported). Significantly more patients, in all age groups, receiving combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 12 compared to patients receiving simvastatin (79 vs 42%; *P*<0.001). Similar results were observed with a LDL-C goal <70 mg/dL (37 vs 6%; *P*<0.001). Treatment-related adverse effects were similar with simvastatin and combination therapy, regardless of dose used and age group (*P* values not reported). Secondary: Not reported
Pearson et al.[62] (2007) Atorvastatin 10, 20, 40, or 80 mg/day for 6 weeks vs simvastatin 10, 20, 40, or 80 mg/day	MA (4 trials) Three identical, prospective 12-week studies randomizing patients to placebo, ezetimibe, ezetimibe with simvastatin or simvastatin alone, and one phase III double-blind, active-controlled study allocating	N=4,373 up to 12 weeks	Primary: Change from baseline in LDL-C level, CRP, proportion of patients reaching LDL-C target (<100 mg/dL or <70 mg/dL) Secondary: Not reported	Primary: Across all doses, patients receiving ezetimibe plus simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the simvastatin monotherapy group (52.5 vs 38%; P<0.001). Across all doses, patients receiving ezetimibe plus simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the atorvastatin monotherapy group (53.4 vs 45.3%; P<0.001). Across all doses, patients on the ezetimibe plus simvastatin combination

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for 12 weeks vs ezetimibe 10 mg/day for 12 weeks vs ezetimibe 10 mg/day added to simvastatin 10, 20, 40, or 80 mg/day for up to 12 weeks vs placebo for 12 weeks	patients to ezetimibe/simvastatin or atorvastatin for 6 weeks			therapy experienced a statistically significant CRP reduction from baseline compared to the simvastatin monotherapy group (31 vs 14.3%; P<0.001). Patients on the ezetimibe plus simvastatin combination therapy experienced a similar CRP reduction from baseline compared to the atorvastatin monotherapy group (25.1 vs 24.8%). The reduction in CRP from baseline was not significantly different between simvastatin 10 mg and placebo groups (P>0.10). Significantly greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (78.9 vs 43.1%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (37 vs 5.7%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the atorvastatin group (79.8 vs 61.9%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the atorvastatin group (36.2 vs 16.8%; P<0.001). Secondary: Not reported
Ansquer et al.[63] (2009) Ezetimibe 10 mg QD and fenofibrate (Tricor®) 145 mg QD vs	DB, MC, RCT Patients 18 to 70 years of age with type IIb dyslipidemia (LDL-C ≥160 mg/dL, TG 150-405 mg/dL) and ≥2 features of the metabolic syndrome	N=60 12 weeks	Primary: Percentage change from baseline in TG and HDL-C Secondary: Percentage change in LDL-C, non-HDL-C, remnant-	Primary: Fenofibrate plus ezetimibe and fenofibrate reduced TG by -38.3% (P value not significant) and increased HDL-C to a similar extent (11.5 and 7.9%, respectively; P=0.282). Secondary: Fenofibrate plus ezetimibe reduced LDL-C by -36.2% compared to -22.4% with fenofibrate and -22.8% with ezetimibe (P<0.001 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ezetimibe 10 mg QD vs fenofibrate (Tricor®) 145 mg QD	according to the NCEP ATP III definition		like particle cholesterol (RLP-C) and related parameters, change in glucose metabolism parameters, hsCRP, safety	Fenofibrate plus ezetimibe lowered non-HDL-C by -36.2% compared to fenofibrate (-24.8%) and ezetimibe (-20.9%) (P value not reported). There was no significant difference between fenofibrate plus ezetimibe and fenofibrate with regards to RLP-C (-36.2 vs -30.7%; P value not significant). Ezetimibe was less effective than fenofibrate plus ezetimibe (-17.3%; P<0.001). The effect of fenofibrate plus ezetimibe on LDL particle size (+2.1%) was similar to that of fenofibrate (+1.9%). Fenofibrate plus ezetimibe was more effective than monotherapy with fenofibrate or ezetimibe in reducing apo B (-33.3%). Fenofibrate plus ezetimibe had the same effect as fenofibrate on apo AI (+7.9 vs +5.1%, respectively) and apo AII (+24.2 vs +21.2%, respectively; P value not reported). Fenofibrate plus ezetimibe and fenofibrate reduced hsCRP to a similar degree. There was a higher incidence of treatment-related adverse events with fenofibrate/ezetimibe, which was primarily due to abnormal laboratory changes, including moderate increases in CK, liver enzymes, and blood creatinine.
Coll et al.[64] (2006) Ezetimibe 10 mg QD vs fluvastatin XR 80 mg QD	RCT HIV patients, ≥6 months on stable HAART, ≥18 years of age, fasting LDL-C ≥3.30 mmol/L	N=20 6 weeks	Primary: LDL-C, TC, endothelial function Secondary: Not reported	Primary: Ezetimibe-treated patients experienced a 20% (P=0.002) LDL-C reduction and a 10% TC reduction (P=0.003). Fluvastatin-treated patients experienced a 24% LDL-C reduction (P=0.02) and a 17% TC reduction (P=0.06). There were no significant differences in lipid-lowering ability between groups. Ezetimibe-treated patients did not experience significant changes in endothelial function. Fluvastatin-treated patients experienced an increase in the rate of endothelial function by 11% (P=0.5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Stein et al.[65] (2004) Ezetimibe 10 mg QD and atorvastatin 10 mg QD (titrated up to 40 mg/day) vs atorvastatin 20 mg QD (titrated up to 80 mg/day)	DB, DD, MC Patients ≥18 years of age with primary hypercholesterolemia and documented CHD, ≥2 cardiovascular risk factors, or heFH with an LDL-C level ≥130 mg/dL despite treatment with atorvastatin 10 mg	N=621 14 weeks	Primary: Percentage of patients achieving an LDL-C level ≤100 mg/dL after 14 weeks randomization Secondary: Effects on other lipid parameters four weeks after randomization	Primary: When compared to atorvastatin monotherapy, a significantly higher percentage of patients in the ezetimibe and atorvastatin reached an LDL-C level ≤100 mg/dL after 14 weeks randomization, respectively (7 vs 22%; P<0.01). Secondary: When compared to atorvastatin monotherapy, significant reductions in LDL-C, TC and TG levels were observed in patients in the ezetimibe and atorvastatin (P<0.01). Respectively, percent changes between combination vs atorvastatin monotherapy were -22.8 vs -8.6% (mean change) in LDL-C levels, -17.3 vs -6.1% in TC levels (mean change), and -9.3 vs -3.9% (median change) in TG levels (P<0.01 for all). Nonsignificant changes were observed in HDL-C levels.
Piorkowski et al.[66] (2007) Ezetimibe 10 mg QD and atorvastatin 10 mg QD vs atorvastatin 40 mg QD	RCT Patients 18 to 80 years of age with clinically stable angiographically documented CHD and LDL-C >2.5 mmol/L despite ongoing atorvastatin 10 to 20 mg/day, receiving aspirin and clopidogrel	N=56 4 weeks	Primary: Change in liver transaminases, CK, HDL-C, LDL-C, and TG from baseline, percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL-C in either group. Both groups exhibited a statistically significant reduction in LDL-C from baseline (P<0.005). There was no statistically significant difference between the two groups in degree of LDL-C reduction from baseline. Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in TG level from baseline (P<0.005 and P<0.05, respectively). There was no statistically significant difference between the two groups in the percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L). Secondary: Not reported
Zieve et al.[67]	DB, MC, PG, RCT	N=1.053	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) ZETELD Ezetimibe 10 mg QD for 12 weeks and atorvastatin 10 mg QD for 6 weeks, followed by atorvastatin 20 mg QD for 6 weeks vs atorvastatin 20 mg QD for 6 weeks, followed by atorvastatin 40 mg for 6 weeks	Patients ≥65 years of age at high risk for CHD with or without AVD who had not reached a LDL-C <70 mg/dL or <100 mg/dL, respectively, after receiving atorvastatin 10 mg/day	12 weeks	Percent change in LDL-C after six weeks Secondary: Percentage of patients achieving LDL-C <70 mg/dL and <100 mg/dL for high-risk patients without AVD and <70 mg/dL for high-risk patients with AVD, HDL-C, non-HDL-C, TG, TG, apo B, apo AI, TC:HDL-C, apo B:apo AI, LDL-C:HDL-C, non-HDL-C:HDL-C	After six weeks of therapy, treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to atorvastatin monotherapy (-29 vs -15%; P<0.001). Secondary: The percentage of patients achieving LDL-C <70 mg/dL and LDL-C <100 mg/dL (without AVD) or <70 mg/dL (with AVD) was significantly greater with ezetimibe plus atorvastatin compared to atorvastatin monotherapy at week six and week 12 (P<0.001). After six weeks of therapy, treatment with ezetimibe plus atorvastatin led to significantly greater changes in HDL-C (+3 vs +1%; P=0.02), TC (-16 vs -8%; P<0.001), non-HDL-C (-24 vs -11%; P<0.001), TG (-13 vs -6%; P<0.001), apo B (-17 vs -8%; P<0.001), TC:HDL-C (-17 vs -8%; P<0.001), LDL-C:HDL-C (-27 vs -13%; P<0.001), apo B:apo AI (-15 vs -5%; P<0.001), and non- HDL-C:HDL-C (-24 vs -11%; P<0.001). At week 12, significantly greater changes in favor of ezetimibe plus atorvastatin occurred in HDL-C, TC, non-HDL-C, apo B, apo AI, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C. There was no significant difference among the treatment groups in apo AI at week six, high-sensitivity C-reactive protein at weeks six and 12, and TG at week 12.
Conard et al.[68] (2008) Ezetimibe 10 mg QD and atorvastatin 20 mg QD vs atorvastatin 40 mg QD	DB, MC, PG, RCT Patients 18 to 79 years of age at moderately high risk for CHD who were receiving atorvastatin 20 mg QD with LDL-C levels of 100 mg/dL to 160 mg/dL and TG ≤350 mg/dL	N=196 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <100 mg/dL, percent change TG, TC, HDL-C, non-HDL-C, apo AI, apo B, TC: HDL-C, LDL-	Primary: Treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-31 vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe plus atorvastatin achieved the NCEP ATP III LDL-C goal <100 mg/dL compared to atorvastatin 40 mg (84 vs 49%, P<0.001). Treatment with ezetimibe plus atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C than treatment with atorvastatin 40 mg (P<0.001).

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			C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C, hsCRP	There was no significant difference in HDL-C, TG, apo AI, and hsCRP among the treatment groups.
Leiter et al.[69] (2008) Ezetimibe 10 mg QD and atorvastatin 40 mg QD vs atorvastatin 80 mg QD	DB, MC, PG, RCT Patients 18 to 79 years of age at high risk for CHD (CHD or those with a CHD risk equivalent medical condition) who were receiving atorvastatin 40 mg QD with LDL-C levels of 70 mg/dL to 160 mg/dL and TG ≤350 mg/dL	N=579 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <70 mg/dL, percent change TG, TC, HDL-C, non-HDL-C, apo AI, apo B, TC: HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C, hsCRP	Primary: Treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-27 vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe plus atorvastatin achieved the NCEP ATP III LDL-C goal <70 mg/dL compared to atorvastatin 80 mg (74 vs 32%, respectively; P<0.001). Treatment with ezetimibe plus atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C compared to atorvastatin 80 mg (P<0.001). There was no significant difference in HDL-C, TG, apo AI, and hsCRP among the treatment groups.
Conrad et al.[70] (2010) Atorvastatin 40 mg/day plus ezetimibe 10 mg/day vs atorvastatin 80 mg/day	DB, MC, PG, RCT Patients 18 to 80 years of age at NCEP ATP III high risk with CHD or CHD risk equivalent, LDL-C ≥70 and ≤160 mg/dL and taking a stable dose of a statin of equal or lesser potency than atorvastatin 40 mg/day or were taking atorvastatin 40 mg/day with good adherence or were stain, ezetimibe	N=568 6 weeks	Primary: Proportion of patients reaching LDL-C <70 mg/dL; percent changes from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, apo AI, TC:HDL-C, LDL-C/HDL-C, apo B/AI, non-HDL-C/HDL-C and hsCRP Secondary:	Primary: The proportion of patients reaching LDL-C <70 mg/dL was greater with combination therapy, with a larger between-treatment difference in proportions in patients with metabolic syndrome (without type 2 diabetes) compared to patients with type 2 diabetes or neither condition, which had similar between-treatment differences in proportions. In patients with type 2 diabetes, metabolic syndrome and those with neither condition, the reduction in LDL-C was greater in patients treated with combination therapy compared to doubling the dose of atorvastatin. The mean between-treatment difference (95% CI) was -17.4 (-21.7 to -13.1), -16.0 (-22.3 to -9.6) and -14.3% (-20.9 to -7.8). Reductions in TC, non-HDL-C and apo B were greater with combination therapy in all three patient populations. The magnitude of the differences between treatments in TG was numerically greater in patients with type 2

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	or ezetimibe/simvastatin naïve		Adverse events	diabetes compared to the other two patient populations, but overall the differences were relatively small. There were no appreciable changes or between-treatment differences in HDL-C and apo AI in any patient population. The percent reduction in lipid ratios was greater with combination therapy in all three patient populations and between-treatment differences were consistent. Combination therapy resulted in numerically greater reductions from baseline in hsCRP in all three patient populations. The between-treatment differences in patients with metabolic syndrome (-11.8) and type 2 diabetes (-10.3) were larger than in patients with neither condition (-3.2). Secondary: There were comparable proportions of patients with one or more adverse event in the type 2 diabetes and metabolic syndrome populations regardless of treatment. The most commonly reported adverse events were gastrointestinal related.
Uemura et al.[71] (2012) Ezetimibe 10 mg/day plus atorvastatin 10 mg/day vs atorvastatin 20 mg	AC, DB, OL, PRO, XO Patients with impaired glucose tolerance or type 2 diabetes who were receiving atorvastatin (10 mg/day) for dyslipidemia, and had CAD with angiographic stenosis (≥50% diameter stenosis on quantitative coronary angiography) or a history of coronary revascularization for stable angina	N=39 24 weeks	Primary: Change from baseline in MDA-LDL, HDL, triglycerides, apo AI, apo B, and RLP Secondary: Not reported	Primary: Ezetimibe plus atorvastatin significantly reduced the serum concentration of MDA-LDL from 109.0±31.9 IU/L at baseline to 87.7±29.4 IU/L after 12 weeks (P=0.0009). The MDA-LDL was not significantly decreased in patients receiving atorvastatin monotherapy (from 109.0±31.9 IU/L to 106.0±34.9 IU/L (P value not significant)). The MDA-LDL level was significantly lower after treatment with ezetimibe plus atorvastatin compared to monotherapy with a higher dose of atorvastatin (P=0.0006). Both treatments significantly improved HDL from baseline (P<0.05 for both); however, there was no difference between the treatment groups (P>0.05). There were no statistically significant differences between combination therapy and atorvastatin monotherapy with regard to a reduction in serum triglycerides (P>0.05). Both treatment regimens significantly reduced total cholesterol from baseline (P<0.05 for both comparisons); however, combination therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reduced total cholesterol significantly further than atorvastatin monotherapy (147.8±21.3 vs 164.3±25.8 mg/dL; P<0.05). Combination treatment with ezetimibe and atorvastatin increased apo AI compared to baseline (P<0.05). Both treatment groups reduced apo B compared to their respective baseline values (P<0.05 for both). Combination therapy was associated with a statistically significant reduction in apo B compared to atorvastatin monotherapy (73.9±18.0 mg/dL vs 83.7±17.2 mg/dL, respectively; P<0.05). A significantly lower apo B/apo AI ratio was achieved with combination therapy compared to atorvastatin monotherapy (P<0.05). No statistically significant difference occurred between combination therapy and atorvastatin monotherapy with regard to RLP-cholesterol (P>0.05).
Constance et al.[72] (2007) Atorvastatin 20 mg QD for 6 weeks, following a 4 week atorvastatin 10 mg QD run-in period vs ezetimibe 10 mg QD added to simvastatin 20 mg QD for 6 weeks, following a 4 week atorvastatin 10 mg QD run-in period vs	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, HbA_{1c} ≤10%, ALT/AST levels <1.5 times the upper limit of normal, CK <1.5 times the upper limit of normal	N=661 6 weeks	Primary: Change from baseline in LDL-C at six weeks Secondary: Change from baseline in TC, HDL-C, TG, non-HDL-C, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio	Primary: Across all doses, patients on the ezetimibe plus simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the atorvastatin 20 mg monotherapy group (P≤0.001). Secondary: Across all doses, patients on the ezetimibe plus simvastatin combination therapy experienced a statistically significant reduction from baseline in TC, non-HDL, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio compared to the atorvastatin 20 mg monotherapy group (P≤0.001). Patients on the ezetimibe 10 mg plus simvastatin 40 mg combination therapy experienced a statistically significant reduction in CRP from baseline compared to the atorvastatin 20 mg monotherapy group (P=0.006). Significantly greater proportion of patients randomized to the ezetimibe 10 mg plus simvastatin 20 mg and ezetimibe 10 mg and simvastatin 40 mg combination therapy achieved LDL-C <2.5 mmol/L, compared to the atorvastatin 20 mg group (90.5, 87, and 70.4%, respectively; P≤0.001).

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ezetimibe 10 mg QD added to simvastatin 40 mg QD for 6 weeks, following a 4 week atorvastatin 10 mg QD run-in period				The incidence of drug-related adverse effects was similar in the ezetimibe/simvastatin 10/20 mg and 10/40 mg combination therapy and atorvastatin monotherapy groups (0.5, 0.5, and 2.3%, respectively).
Hing Ling et al.[73] (2012) Atorvastatin 40 mg/day vs ezetimibe 10 mg/day plus simvastatin 40 mg/day All patients received atorvastatin 20 mg/day for six weeks at baseline.	AC, DB, MC, RCT Patients 18 to 79 years of age at high risk for CHD with primary hypercholesterolemia, LDL >100 mg/dL and <160 mg/dL, triglycerides <350 mg/dL, liver function tests within normal limits without active liver disease	N=250 6 weeks	Primary: Change from baseline in LDL-C, Secondary: TC, HDL, CRP, Apo AI, Apo B, TG, non-HDL, LDL-C/HDL ratio, TC/HDL ratio, non-HDL/HDL ratio, Apo AI/Apo B ratio	Primary: After six weeks, treatment with ezetimibe/simvastatin resulted in significantly greater reductions from baseline in LDL-C levels compared to treatment with atorvastatin 40 mg (-26.8 vs -11.8%; P<0.001). Secondary: Treatment with ezetimibe/simvastatin resulted in significantly greater reductions in TC (P<0.001), non-HDL-C (P<0.001), Apo B (P=0.002), Apo AI (P<0.001), and all lipid ratios (P<0.001 for all). There were no significant differences between treatments with regard to the change from baseline in TG (P=0.593), HDL-C (P=0.211), or CRP (P=0.785).
Bays et al.[74] (2013) PACE Period I: adding ezetimibe 10 mg to stable atorvastatin 10 mg vs	AC, DB, RCT Patients aged ≥18 and <80 years with primary hypercholesterolemia at high CV risk, lipid-lowering therapy naïve with an LDL-C between 166 and 190 mg/dL, or on a stable dose of statin,	N=1,547 12 weeks	Primary: Percent change from treated baseline in LDL-C levels at the end of period I Secondary: Percent change from treated baseline in LDL-C	Primary: The addition of ezetimibe to atorvastatin 10 mg produced a greater reduction in LDL-C than doubling the atorvastatin dose to 20 mg or switching to rosuvastatin 10 mg (-22.2, -9.5, and -13.0, respectively; P<0.001, both groups). Secondary: The addition of ezetimibe to atorvastatin 10 mg produced significantly greater attainment of LDL-C <100 or <70 mg/dl and significantly greater reductions in total cholesterol, non–HDL cholesterol, apo B, and LDL-C/HDL-C, total/HDL-C, and non-HDL-C/HDL-C ratios than atorvastatin

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doubling atorvastatin to 20 mg vs switching to rosuvastatin 10 mg Subjects in the latter 2 groups who persisted with elevated LDL-C levels (≥100 and ≤160 mg/dL) after period I, entered period II: subjects on atorvastatin 20 mg had ezetimibe added to their atorvastatin, or uptitrated atorvastatin to 40 mg; subjects on rosuvastatin 10 mg switched to atorvastatin 20 mg plus ezetimibe or uptitrated rosuvastatin to 20 mg	ezetimibe, or statin plus ezetimibe having LDL-C-lowering efficacy equivalent to or less than atorvastatin 10 mg After enrollment all patients were administered atorvastatin 10 mg daily as only lipid-lowering therapy for 5 weeks		at the end of period II; percentage of subjects achieving LDL-C <100 or <70 mg/dl at the end of periods I and II; percent change from treated baseline in other lipids, lipoproteins, and high-sensitivity C-reactive protein (hsCRP) at the end of periods I and II; assessment of safety and tolerability	20 mg or rosuvastatin 10 mg. The change from baseline in HDL-C, triglycerides, apo AI, and hsCRP were similar among treatments. At the end of period II, ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than atorvastatin 40 mg (17.4 vs 6.9%, P<0.001); switching from rosuvastatin 10 mg to ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than uptitrating to rosuvastatin 20 mg (17.1 vs 7.5%, P<0.001). All treatments were generally well-tolerated.
Goldberg et al.[75] (2006)	DB, MC, PG, RCT	N=1,229	Primary: Percent reduction	Primary: Patients randomized to simvastatin 20 mg plus ezetimibe 10 mg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
VYTAL Atorvastatin 10, 20, or 40 mg/day vs simvastatin 20 or 40 mg/day and ezetimibe 10 mg/day	Adult patients with type 2 diabetes between 18 and 80 years of age with HbA_{1c} ≤8.5%, LDL-C >100 mg/dL and a TG level <400 mg/dL	6 weeks	in LDL-C level at week six Secondary: Proportion of patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of patients who achieved LDL-C level of <100 mg/dL, percent change from baseline in HDL-C, non-HDL-C, TC, TG, and CRP	combination therapy experienced a greater reduction in LDL-C from baseline at week six of the study compared to patients receiving atorvastatin 10 or 20 mg (53.6, 38.3, and 44.6%, respectively; P<0.001). Patients randomized to simvastatin 40 mg plus ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week six of the study compared to patients receiving atorvastatin 40 mg (57.6 and 50.9%, respectively; P<0.001). Secondary: A greater proportion of patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy achieved LDL-C <70 mg/dL compared to patients receiving atorvastatin 10 or 20 mg (59.7, 21.5, and 35%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 40 mg plus ezetimibe 10 mg therapy achieved LDL-C <70 mg/dL compared to patients receiving atorvastatin 40 mg (74.4 and 55.2%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 20 mg plus ezetimibe 10 mg therapy achieved LDL-C <100 mg/dL compared to patients receiving atorvastatin 10 or 20 mg (90.3, 70, and 82.1%, respectively; P=0.007). A greater proportion of patients randomized to simvastatin 40 mg plus ezetimibe 10 mg therapy achieved LDL-C <100 mg/dL compared to patients receiving atorvastatin 40 mg (93.4 and 88.8%, respectively; P=0.07). Patients randomized to simvastatin plus ezetimibe combination therapy, at all doses, experienced a significant increase in HDL-C level (P≤0.001), a greater reduction in TC, and non-HDL-C (P<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy experienced a significant reduction in CRP and TG

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				level compared to patients receiving atorvastatin (P=0.02). Side effects were similar in the simvastatin plus ezetimibe and atorvastatin groups (19.85 vs 22.7%).
Kumar et al.[76] (2009) Ezetimibe 10 mg/day plus fenofibrate 160 mg/day vs atorvastatin 10 mg/day	RCT, XO Patients with hypercholesterolemia requiring pharmacotherapy	N=43 12 weeks	Primary: Percentage reduction of LDL-C Secondary: Percent changes from baseline in TC, HDL-C and TG	Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (P=0.46). Secondary: Both treatments provided similar improvements in TC (-25.1 vs -24.6%; P=0.806) and HDL-C (10.1 vs 8.9%; P=0.778). Combination therapy showed a trend towards a greater reduction in TGs (25.4 vs 14.5%; P=0.079), although there were no significant difference between the two treatments in terms of the improvement in TC:HDL-C (-29.0 vs -28.7%; P=0.904).
Stojakovic et al.[77] (2010) Ezetimibe 10 mg/day plus fluvastatin 80 mg/day vs fluvastatin 80 mg/day	PRO, RCT, SB Patients with CHD or CHD risk equivalent with LDL-C 100 to 160 mg/dL	N=90 12 weeks	Primary: Changes from baseline in lipids, apolipoproteins and lipoprotein subfractions Secondary: Not reported	Primary: After 12 weeks, TC, LDL-C and apo B were significantly lowered with both treatments, but the reductions were significantly greater with combination therapy (P<0.001 for all). Combination therapy significantly reduced TG, apo CII, apo CIII and apo E compared to baseline (P<0.001 for all) and fluvastatin (P=0.008, P=0.002 and P=0.007). Apo AI and AII increased with fluvastatin and decreased with combination therapy. Accordingly, HDL-C increased with fluvastatin and decreased with combination therapy, but the difference was not significant (P=0.080). Similar results were observed when only patients with type 2 diabetes were analyzed. Secondary: Not reported
Stein et al.[78] (2008) Fluvastatin XL 80 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with dyslipidemia who had previously documented muscle	N=218 12 weeks	Primary: Percent decrease in LDL-C Secondary: LDL:HDL-C, TC,	Primary: LDL-C was reduced by 15.6, 32.8, and 46.1% with ezetimibe monotherapy, fluvastatin XL monotherapy, and fluvastatin XL plus ezetimibe combination therapy, respectively (fluvastatin XL vs ezetimibe: -17.1%, P<0.0001; fluvastatin XL plus ezetimibe vs ezetimibe: -30.4%, P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ezetimibe 10 mg QD vs fluvastatin XL 80 mg QD and ezetimibe 10 mg QD	related side effects that had led to cessation of statin treatment or patients currently receiving statin treatment whose quality of life was affected by muscle related side effects and required switching to an alternative treatment		TG, apo B, proportion of patients achieving LDL-C goal	Secondary: Treatment with fluvastatin XL monotherapy and fluvastatin XL plus ezetimibe combination therapy led to a greater reduction in LDL:HDL-C, TC, TG, and apo B levels compared to ezetimibe monotherapy (all, P<0.0001). More patients achieved their target LDL-C goal with fluvastatin XL monotherapy and fluvastatin XL plus ezetimibe combination therapy compared to ezetimibe monotherapy (P<0.001 for fluvastatin XL monotherapy or combination therapy vs ezetimibe monotherapy). There were no serious adverse events, rhabdomyolysis, or creatine kinase increases ≥10 times upper limit of normal. Muscle related side effects were reported in 24% of patients receiving ezetimibe monotherapy compared to 17% of patients in the fluvastatin XL group and 14% of patients in the fluvastatin XL plus ezetimibe combination group. Differences in recurrence of muscle related side effects were not statistically different between treatment groups.
Alvarez-Sala et al.[79] (2008) Fluvastatin XL 80 mg QD (nighttime) and ezetimibe 10 mg QD vs fluvastatin XL 80 mg QD (nighttime)	MC, OL, PG, RCT Patients 18 to 75 years of age with primary hypercholesterolemia (LDL-C ≥130 mg/dL and TG ≤400 mg/dL)	N=89 12 weeks	Primary: Percentage change in LDL-C Secondary: Percentage change in HDL-C and TG, proportions of patients achieving NCEP ATP III LDL-C goals, change in hsCRP and other markers of inflammation, and safety	Primary: Fluvastatin XL plus ezetimibe lowered mean LDL-C from 197 mg/dL to 97 mg/dL (-49.9%) and fluvastatin XL alone lowered mean LDL-C from 216 to 135 mg/dL (-35.2%) after 12 weeks of therapy (P<0.001). Secondary: Fluvastatin XL plus ezetimibe combination was associated with a significantly greater reduction from baseline in TC, TG, and apo B than fluvastatin XL alone (P<0.05 for all). There was no significant change in HDL-C level with either treatment regimen. A greater proportion of patients receiving the fluvastatin XL plus ezetimibe achieved NCEP ATP III LDL-C goals at week 12 compared to those receiving fluvastatin XL alone (86.5 vs 66.7%; P=0.042). There were no significant changes in levels of hsCRP with either treatment regimen. In patients with higher baseline hsCRP levels, the coadministration of fluvastatin XL with ezetimibe was associated with a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reduced level of this inflammatory marker. Treatment with fluvastatin XL plus ezetimibe or fluvastatin XL alone was associated with significant reductions in IL-1β (21%; P<0.001 and 13%; P<0.002, respectively). No significant changes were seen in levels of interleukin-6, tumor necrosis factor-α, soluble P-selectin, or soluble vascular cell adhesion molecule-1. There was no significant difference in the incidence of adverse events between the treatment groups. Most adverse events were mild or moderate in intensity, with headache being the most common (8.5%).
Winkler et al.[80] (2009) Fluvastatin 80 mg/day plus fenofibrate 200 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 mg/day	MC, OL, RCT, XO Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist circumference ≥94 (men) or ≥80 cm (females) plus 1 of the following: TG ≥150 mg/dL, BP (≥85/≥130 mm Hg), fasting glucose ≥100 mg/dL or prevalent type 2 diabetes	N=75 6 weeks	Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions Secondary: Not reported	Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only reached significance in patients without small, dense LDL (P=0.043, P=0.006 and P=0.20). Reductions in TG were only significant with fluvastatin plus fenofibrate compared to ezetimibe plus simvastatin in patients with small, dense LDL (P=0.029). Increases in HDL-C and apo AI were only significant with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate in patients without small, dense LDL (P=0.020 and P=0.015). In patients with small, dense LDL, apo AII was markedly increased by fluvastatin plus fenofibrate, whereas ezetimibe plus simvastatin had no or little effect. Although only significant in small, dense LDL patients, apo CIII was more effectively reduce by fluvastatin plus fenofibrate, while the reduction of apo CII was more pronounced with ezetimibe plus simvastatin in all patients. Secondary: Not reported
Ballantyne et al.[81] (2007) EXPLORER Ezetimibe 10 mg QD and rosuvastatin 40 mg QD	MC, OL, PG, RCT Men and women aged ≥18 years with hypercholesterolemia, history of CHD or clinical evidence of atherosclerosis or CHD	N=469 6 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal (<100 mg/dL) after 6 weeks of treatment	Primary: Significantly more patients in the combination therapy group achieved the LDL-C goal of <100 mg/dL at week six compared to rosuvastatin alone (94 vs 79.1%; P<0.001). Secondary: The non-HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL were achieved by a significantly higher

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rosuvastatin 40 mg QD	risk equivalent (10-year CHD risk score >20%), 2 most recent fasting LDL-C levels of ≥160 mg/dL and <250 mg/dL		Secondary: Percentage of patients achieving the ATP III non-HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL, percentage of patients achieving the 2003 European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals of <100 or 115 mg/dL and <175 or 190 mg/dL, respectively, depending on risk category, percentage change from baseline in LDL, HDL, TC, TG, non-HDL, lipid ratios (LDL:HDL, TC:HDL and non-HDL:HDL), apo AI, apo B, and apo B:apo AI ratio, and changes in hsCRP in at week 6, safety and tolerability	percentage of patients in the combination therapy group than the monotherapy group (88 patients or 37.4% and 80 patients or 34.8%, respectively; P<0.001). There was a significantly higher percent of patients in the combination therapy group achieving the European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals (LDL <100 or 115 mg/dL and TC <175 or 190 mg/dL), depending on risk category compared to the rosuvastatin group alone at week six (LDL 93.6 vs 74.3%, LDL and TC 90.6 vs 68.3%, respectively; P<0.001). At week six, the combination therapy group had a significantly greater percent reduction of 69.8% in the LDL level compared to a 57.1% reduction in the monotherapy group (P<0.001). Significantly greater reductions in TC, non-HDL-C and TG levels were seen in the combination group compared to the monotherapy group (P<0.001). Both treatment groups increased HDL level to a similar extent (P=0.151). LDL:HDL, TC:HDL and non-HDL:HDL cholesterol ratios decreased significantly more in patients receiving combination therapy compared to patients receiving monotherapy (all P<0.001). Significant decreases in apo B and the apo B:apo AI ratios were seen in the combination therapy group compared to the monotherapy group (P<0.001 for both). Apo AI increased by 3.2% and 1.6% in the combination therapy and monotherapy groups, respectively (P=0.202). The median percent decrease in CRP was significantly higher with combination therapy than monotherapy (-46.4 vs -28.6%; P<0.001). The overall frequency and type of adverse events were similar in both groups, with 31.5% of patients on combination therapy and 33.5% of patients on monotherapy reporting any adverse event. No adverse events were considered related to ezetimibe; the most frequently reported adverse event was myalgia (3.0% of patients in the rosuvastatin-alone group and 2.9% in the rosuvastatin plus ezetimibe group). There were two patients (0.8%) in the combination therapy group and three patients (1.3%) in the monotherapy group who discontinued the study due to treatment-related adverse events. One death occurred in the combination therapy group due to acute myocardial infarction and this was not considered to be related to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				study treatment. ALT increases >3 times the upper limit of normal were recorded in three patients, all in the combination therapy group.
Chenot et al.[82] (2007) Simvastatin 40 mg/day vs ezetimibe 10 mg/day and simvastatin 40 mg/day vs no lipid-lowering therapy	RCT Patients, average age 61 years, admitted for an acute MI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission	N=60 7 days	Primary: Change from baseline in LDL-C at days 2, 4 and 7, and the achievement of LDL-C <70 mg/dL Secondary: Not reported	Primary: Patients receiving ezetimibe plus simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline on days two, four, and seven (27, 41, and 51%, respectively; P<0.001). Patients on the simvastatin monotherapy experienced a statistically significant LDL-C reduction from baseline on days two, four, and seven (15, 27, and 25%, respectively; P<0.001). There was no statistically significant change from baseline in LDL-C in the no lipid-lowering therapy group (P≥0.09). Patients on the ezetimibe plus simvastatin combination therapy achieved lower LDL-C levels compared to the simvastatin monotherapy group at day four (P=0.03) and day seven (P=0.002) of the study. A greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin monotherapy group at day four and day seven (45 vs 5, and 55 vs 10%, respectively). Secondary: Not reported
Gaudiani et al.[83] (2005) Simvastatin 20 mg/day and ezetimibe 10 mg/day vs simvastatin 40 mg/day	DB, MC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes (HbA_{1c} ≤9.0%), treated with a stable dose of pioglitazone (15 to 45 mg/day) or rosiglitazone (2 to 8 mg/day) for ≥3 months, LDL-C >100	N=214 30 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and	Primary: LDL-C was reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin (20.8 vs 0.3%; P<0.001). Secondary: TC (14.5 vs 1.5%; P<0.001), non-HDL-C (20.0 vs 1.7%; P<0.001), apo B (14.1 vs 1.8%; P<0.001), LDL-C:HDL-C (P<0.001), TC:HDL-C (P<0.001) and apo AI (P<0.001) were reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin. The increase in HDL-C was similar between the two treatments (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received simvastatin 20 mg/day for a 6 week run in period.	mg/dL and TG <600 mg/dL (if already on a statin therapy)		apo AI	The incidence of treatment-related adverse effects was lower with simvastatin compared to combination therapy (10.0 vs 18.3%, respectively; P value not reported).
Feldman et al.[84] (2004) Ezetimibe 10 mg/day plus simvastatin 10, 20, or 40 mg/day vs simvastatin 20 mg/day	DB, MC, RCT Patients 18 to 80 years of age with CHD or CHD risk equivalent disease and LDL-C ≥130 mg/dL and TG ≤350 mg/dL	N=710 23 weeks	Primary: Proportion of patients with LDL-C <100 mg/dL at week five Secondary: Proportion of patients with LDL-C <100 mg/dL at 23 weeks	Primary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week five compared to patients receiving simvastatin (P<0.001). Secondary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week 23 compared to patients receiving simvastatin (P<0.001). At five weeks, there was a significant reduction in TC, non-HDL-C, apo B, TC:HDL-C and LDL-C:HDL-C with combination therapy compared to simvastatin (P<0.001 for all). HDL-C was significantly increased with combination therapy (10/20 mg) compared to simvastatin (P<0.05). At five weeks, combination therapy was associated with a significant reduction in TG compared to simvastatin (P<0.05). Treatment-related adverse effects were similar with simvastatin and combination therapy (10/10, 10/20 and 10/40 mg) (7.5, 9.6, 14.0 and 10.0%, respectively; P values not reported).
Okada et al.[85] (2011) Ezetimibe 10 mg/day plus atorvastatin 10 mg/day	MC, OL, PG, PRO, RCT Patients ≥20 years of age with CAD whose LDL-C levels were ≥100 mg/dL	N=171 12 weeks	Primary: Change from baseline in LDL-C, HDL, TG, TC, proportion of patients achieving an LDL-C <100	Primary: In both the ezetimibe plus statin group and the double-dose statin group, LDL-C levels decreased from baseline to 12 weeks; however, the decrease was significantly greater in the ezetimibe plus statin group (24.7±12.1 vs -16.4±11.7%; P<0.01). The proportion of patients achieving the LDL-C goal of <100 mg/dL was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ezetimibe 10 mg/day plus rosuvastatin 2.5 mg/day vs atorvastatin 20 mg/day vs rosuvastatin 5 mg/day	after ≥4 weeks of treatment with atorvastatin 10 mg/day or rosuvastatin 2.5 mg/day		mg/dL Secondary: Not reported	significantly higher in the ezetimibe plus statin group compared to doubling the statin dose (76.1 vs 58.9%; P<0.05). The HDL-C level increased in the ezetimibe plus statin group and decreased in the double-dose statin group (2.7±16.6 vs -1.0±17.2%; P<0.05). The triglyceride level decreased for patients receiving ezetimibe plus a statin compared to an increase in triglycerides for patients who received an increased dose of statin (-9.4±30.2 vs 3.1± 40.7%, P<0.05).
Gagné et al.[86] (2002) Statin 40 mg for up to 14 weeks, followed by the addition of ezetimibe 10 mg QD for another 12 weeks, administered as separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily and addition	DB, MC, RCT Patients ≥12 years old (or with body weight ≥40 kg) with hoFH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on atorvastatin or simvastatin 40 mg/day)	N=50 26 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (20.7 vs 6.7%; P=0.007). Secondary: TC was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (18.7 vs 5.3%; P<0.01). There was no statistically significant difference in any of the other secondary outcome measures between the two groups (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of ezetimibe 10 mg QD daily for another 12 weeks, administered as separate vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily Statins used in the study included simvastatin and atorvastatin.				
McKenney et al.[87] (2007) COMPELL Rosuvastatin 10 mg/day for 4 weeks, followed by 20 mg/day for 4 weeks, followed by 40 mg/day vs atorvastatin 20 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by atorvastatin 20 mg/day plus niacin	MC, OL, PG, RCT Patients ≥21 years of age with hyper-cholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL	N=292 12 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects	Primary: Atorvastatin plus niacin SR, rosuvastatin plus niacin SR, simvastatin plus ezetimibe and rosuvastatin were associated with similar reductions in LDL-C (56, 51, 57 and 53%, respectively; P=0.093). Secondary: Atorvastatin plus niacin SR was associated with a significant increase in HDL-C compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (22, 10 and 7%, respectively; P≤0.05). There was no significant differences in the reduction of non-HDL-C from baseline with any treatment (P=0.053). Atorvastatin plus niacin SR was associated with a significant reduction in TG compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (47, 33 and 25%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in Lp(a) compared to simvastatin plus ezetimibe and rosuvastatin (20 mg)-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day vs simvastatin 20 mg/day plus ezetimibe 10 mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10 mg/day vs rosuvastatin 10 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by rosuvastatin 10 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by rosuvastatin 20 mg/day plus niacin SR 1,000 mg/day				containing therapy (-14, 7 and 18%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in apo B compared to rosuvastatin (43 vs 39%, respectively; P≤0.05). Side effects were similar across treatments (P values not reported). There were no cases of myopathy or hepatotoxicity reported.
Cannon et al.[88,89] (2015) ODYSSEY COMBO II	AC, DB, DD, MC, PG, RCT Patients ≥18 years of	N=720 104 weeks	Primary: Percent change in calculated LDL-C from baseline to	Primary: Alirocumab was associated with a significantly greater reduction in mean LDL-C from baseline at week 24 compared to ezetimibe (50.6 ± 1.4% vs 20.7 ± 1.9%; 29.8% ± 2.3% difference; P<0.0001).

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Alirocumab 75 mg injected SC every two weeks (dose increased to 150 mg at week 12 if LDL ≥1.8 mmol/L) vs ezetimibe 10 mg QD Patients continued to take statin therapy. Other lipid lowering therapy was not permitted. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet for the duration of the study.	age with established heart disease or CHD equivalent, LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥ 100 mg/dL and no established heart disease but at a high risk for CVE and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening		week 24 Secondary: Absolute cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations and safety evaluations	Secondary: Seventy seven percent of alirocumab and 45.6% of ezetimibe patients achieved LDL-C <1.8 mmol/L (P<0.0001). As compared with the ezetimibe group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and had a modest increase in levels of HDL-C (P<0.0001 for all comparisons). TG were reduced from baseline to week 24 by 13.0 ± 1.5% in the alirocumab group and by 12.8 ± 2.0% in the ezetimibe group, but the difference between treatment arms was not statistically significant. Alirocumab was generally well tolerated, with no evidence of an excess of treatment-emergent adverse events. Adjudicated cardiovascular events were infrequent, occurring in 4.8% (n=23) of the alirocumab group vs 3.7% (n=9) in the ezetimibe group. Treatment-emergent local injection site reactions occurred in 2.5% of patients in the alirocumab arm vs 0.8% for ezetimibe arm.
Roth et al.[90] (2015) ODYSSEY MONO Alirocumab 75 mg injected SC every	DB, MC, PC, RCT Patients with primary hyper-cholesterolemia and moderate risk for CVE and LDL-C ≥100mg/ dL	N=103 34 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary:	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to ezetimibe (47.2% vs 15.6%; P<0.0001). Secondary: Safety parameters and adverse events were similar between the two groups. The most common class of adverse events was infections (39.2%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
two weeks (dose increased to 150 mg at week 8 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD	and ≤190mg/dL		Safety evaluations	with ezetimibe vs 42.3% with alirocumab), which included nasopharyngitis, influenza, and upper respiratory tract infection. Injection-site reactions occurred in less than 2% of patients in both groups. Muscle-related adverse events occurred in 3.9% of patients treated with ezetimibe and 3.8% of patients treated with alirocumab.
Bays et al.[91,92] (2015) ODYSSEY OPTIONS I Alirocumab 75 mg injected SC every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD vs atorvastatin (at double baseline dose) vs rosuvastatin 40 mg QD (atorvastatin 40 mg baseline	AC, DB, MC, PG, RCT Patients ≥18 years of age with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥ 100 mg/dL and risk factors for CVE	N=355 24 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: Among atorvastatin 20 and 40 mg regimens respectively, there was a significantly greater decrease in LDL-C with alirocumab add-on from baseline at week 24 compared to add-on ezetimibe, double dose atorvastatin and switching to rosuvastatin (44.1% and 54.0% vs 20.5% and 22.6%, 5.0% and 4.8%, and 21.4%; P<0.001 vs all comparators). Most alirocumab-treated patients (86%) maintained their 75 mg every two weeks regimen. Secondary: Treatment-emergent adverse events occurred in 65.4% of alirocumab patients, compare to 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin (data pooled).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose cohort only) Prior to randomization, patients were stabilized on atorvastatin 20 mg to 40 mg QD.				
Moriarty et al.[93] (2015) ODYSSEY ALTERNATIVE Alirocumab 75 mg SC every 2 weeks vs ezetimibe 10 mg/ day vs atorvastatin 20 mg/ day	AC, DB, MC, PG, RCT Patients with primary hypercholesterolemia at moderate to high cardiovascular risk with statin intolerance (unable to tolerate ≥2 statins, including one at the lowest approved starting dose) due to muscle symptoms	N=314 24 weeks	Primary: Percent change in calculated LDL–C from baseline to 24 weeks Secondary: Change from baseline to 24 weeks using on-treatment (modified ITT) LDL-C values, and percent change from baseline to 12 and 24 weeks in LDL-C, apolipoprotein B, non–HDL-C, total cholesterol, lipoprotein(a), HDL-C, apolipoprotein A1, and fasting triglyceride concentrations; adverse events	Primary: For the primary ITT efficacy analysis, LS mean change in LDL-C concentrations from baseline to week 24 were −45.0% for alirocumab and −14.6% for ezetimibe, with a difference between groups of −30.4% (P<0.0001). Secondary: For the on-treatment analysis, the change from baseline was −52.2% for alirocumab and −17.1% for ezetimibe (LS mean difference of −35.1%; P<0.0001). A substantial reduction in LDL-C concentration occurred over the first four weeks, which was greater in the alirocumab arm and persisted throughout the 24-week treatment period. At week 24, 52 (41.9%) patients on alirocumab and 5 (4.4%) of those on ezetimibe (P<0.0001; ITT analysis) reached an LDL-C goal of <70 mg/dL in very high cardiovascular risk patients or <100 mg/dL in moderate-to-high-risk patients. Corresponding results in the on-treatment population were 51.2% and 5.6% (P<0.0001). The greater effect of alirocumab relative to ezetimibe on LDL-C-lowering from baseline to week 24 was consistent across most of the prespecified subgroups in the ITT population. In addition, reductions in apolipoprotein B, non–HDL-C, total cholesterol and lipoprotein(a) concentrations were greater for alirocumab vs ezetimibe (all P<0.0001). There were no statistically significant differences between the two groups in changes in triglyceride, HDL-C, and apolipoprotein A1 concentrations. Overall rates of treatment-emergent and serious AEs were generally similar between treatment arms, and there were no deaths in the study.
Farnier et al.[94] (2016)	DB, DD, MC, RCT	N=305	Primary: Percent change in	Primary: In the baseline rosuvastatin 10 mg regimen ITT analysis, alirocumab add-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ODYSSEY OPTIONS II Add-on alirocumab 75 mg every 2 weeks (1-mL subcutaneous injection via pre-filled pen) vs add-on ezetimibe 10 mg/day vs double-dose rosuvastatin All patients received baseline rosuvastatin regimens (10 or 20 mg)	Patients with cardiovascular disease and LDL–C ≥70 mg/dL or cardiovascular disease risk factors and LDL–C ≥100 mg/dL	24 weeks	calculated LDL–C from baseline to 24 weeks Secondary: Percent change from baseline in calculated LDL–C on-treatment at Week 24 in the modified ITT (mITT) population (on-treatment analysis), percent change in LDL–C from baseline to Week 12 (ITT and on-treatment), the percent change in other lipid parameters, and the proportion of very-high and high CV risk patients reaching LDL–C <70 mg/ or <100 mg/ at Week 24, respectively, in both ITT and on-treatment analyses; Safety	on treatment significantly reduced LDL–C levels at Week 24 versus the other comparators (P<0.0001). From baseline, add-on alirocumab reduced LDL–C by 50.6%, add-on ezetimibe reduced LDL–C by 14.4%, and double-dose (20 mg) rosuvastatin reduced LDL–C by 16.3%. In the baseline rosuvastatin 20 mg regimen ITT analysis, mean reductions from baseline in LDL–C at Week 24 were greater in the alirocumab add-on group versus the other comparators. LDL–C reductions were 36.3% in the add-on alirocumab group, compared with 11.0% in the add-on ezetimibe group (P=0.0136) and with 15.9% in the double-dose (40 mg) rosuvastatin group (P=0.0453). However, the pre-specified threshold P-value for these 4-way comparisons was 0.0125; therefore, both primary comparisons failed to reach statistical significance in the baseline rosuvastatin 20 mg regimen. Secondary: As a result of both primary comparisons failing to reach statistical significance, all key secondary efficacy endpoints were not tested for statistical significance with respect to the two comparisons in the baseline rosuvastatin 20 mg regimen. In the baseline rosuvastatin 10 mg regimen groups, the proportion of patients at very-high and high CV risk who reached a LDL–C level of <70 mg/dL or <100 mg/dL at Week 24, depending on risk status, was significantly greater in the alirocumab add-on group (84.9%) compared with the ezetimibe add-on group (57.2%; P=0.0007) and the rosuvastatin 20 mg group (45.0%; P<0.0001). The proportion of patients who reached the more stringent LDL–C level of <70 mg/dL at Week 24 was also significantly greater in the alirocumab add-on group (77.8%) compared with the ezetimibe add-on and rosuvastatin 20 mg groups (43.1%; P<0.0001 and 31.3%; P<0.0001), respectively. Treatment-emergent adverse events occurred in 56.3% of alirocumab patients versus 53.5% ezetimibe and 67.3% double-dose rosuvastatin (pooled data).
Stroes et al.[95] (2014)	AC, DB, MC, RCT	N=307	Primary: LDL-C at week 12	Primary: Evolocumab reduced LDL-C from baseline by 53% (every two weeks) to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
GAUSS-2 Evolocumab 140 mg injected SC every two weeks vs evolocumab 420 mg injected SQ monthly vs ezetimibe 10 mg QD	Patients 18 to 80 years of age with an LDL-C above ATP III goal and a previous intolerance to ≥2 statins		and mean of weeks 10 and 12 Secondary: Percentage of patients with LDL-C <70 mg/dL, non HDL-C, apoB, apoB/apolipoprotein A1, lipoprotein (a), TG, TC/HDL-C, VLDL and safety evaluations.	56% (monthly), corresponding to treatment differences versus ezetimibe of 37 to 39% (P<0.001). Mean percent reductions from baseline and treatment differences at week 12 were similar (P<0.001). Secondary: Evolocumab-treated patients were more likely to achieve LDL-C target levels than ezetimibe-treated patients. Compared with ezetimibe, evolocumab led to significant reductions in apoB, lipoprotein(a), non–HDL-C and the apoB/apolipoprotein A-I and TC/HDL-C ratios (P<0.001) Muscle adverse events occurred in 12% of evolocumab-treated patients and 23% of ezetimibe-treated patients. Treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups.
Nissen et al.[96] (2016) GAUSS-3 Evolocumab (420 mg monthly subcutaneously) vs ezetimibe (10 mg daily by mouth)	DB, DD, RCT Patients 18 to 80 years of age with elevated LDL-C levels who were unable to tolerate an effective dose of a statin because of muscle-related adverse effects	N=491 24-week crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin but not placebo; followed by 2-week washout; followed by 24-week	Primary: Mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels Secondary: Absolute change from baseline in LDL-C level; percent change from baseline in levels of total cholesterol, non–high-density lipoprotein cholesterol (non–	Primary: Mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels showed a least-squares mean change of −16.7% (95% CI, −20.5 to −12.9%) for ezetimibe and −54.5% (95% CI, −57.2 to −51.8%) for evolocumab: a mean difference of −37.8% (95% CI, −42.3 to −33.3%; P<0.001). Mean percent change in LDL-C level from baseline to the week 24 showed a least-squares mean change of −16.7% (95% CI, −20.8 to −12.5%) for ezetimibe and −52.8% (95% CI, −55.8 to −49.8%) for evolocumab: a mean difference of −36.1% (95% CI, −41.1 to −31.1%; P<0.001). Secondary: Secondary end points including percent changes in levels of total cholesterol, non–HDL-C, and ApoB; total cholesterol to HDL-C ratio; and ApoB to apolipoprotein A1 ratio showed similar results, with P<0.001 demonstrating greater cholesterol reductions in the evolocumab group. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (P=0.17). Active study drug

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
		comparison	HDL-C), and apolipoprotein B (ApoB); percent change from baseline in total cholesterol to HDL-C ratio and ApoB to apoliprotein A1 ratio; and the percentage of patients achieving an LDL-C level less than 70 mg/dL; safety	was stopped for muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%).
Trials Assessing Atherosclerosis Progression and Cardiovascular Outcomes				
Kastelein et al.[97] (2008) ENHANCE Ezetimibe 10 mg QD vs placebo All patients received simvastatin 80 mg QD.	DB, MC, PC, PRO, RCT Men and women between the ages of 30 and 75 years with familial hypercholesterolemia regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C ≥210 mg/dL without treatment	N=720 24 months	Primary Change in mean CIMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of patients with regression in the mean CIMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm with placebo and 0.0111±0.0038 mm with ezetimibe (P=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4 vs 45.3%; P=0.92) or new plaque formation (2.8 vs 4.7%; P=0.20) receiving placebo vs ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 and 0.0175±0.0049 mm, respectively; P=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (P=0.93), carotid bulb (P=0.37), internal carotid artery (P=0.21) and femoral artery (P=0.16) or average of the mean values for carotid and femoral artery IMT (P=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			maximal carotid artery IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	group and by 55.6 mg/dL in the ezetimibe group (between-group difference of 16.5%; P<0.01). Reductions in TG (between-group difference of 6.6%; P<0.01) and CRP (between-group difference of 25.7%; P<0.01) were significantly higher with ezetimibe compared to placebo. Adverse events (29.5 vs 34.2%; P=0.18) and discontinuation rates (9.4 vs 8.1%; P=0.56) were similar between placebo and ezetimibe.
Rossebø et al.[98] (2008) SEAS Ezetimibe 10 mg QD and simvastatin 40 mg QD vs placebo OL lipid-lowering therapy, which included up to 40 mg of simvastatin or an equipotent dose of another lipid-lowering drug, could be administered in addition to the study drug at the discretion of each treating physician.	DB, MC, RCT Patients 45 to 85 years of age who had asymptomatic, mild-to-moderate aortic valve stenosis with a peak aortic-jet velocity of 2.5 to 4 m per second	N=1,873 52.2 months (median duration)	Primary: Composite of major cardiovascular events (death from cardiovascular causes, aortic-valve replacement, CHF as a result of progression of aortic-valve stenosis, nonfatal MI, hospitalization for unstable angina, CABG, PCI, non-hemorrhagic stroke) Secondary: Aortic-valve events, progression of aortic stenosis, safety	Primary: The composite of major cardiovascular events occurred in 35.3% of patients in the simvastatin plus ezetimibe group and in 38.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.83 to 1.12; P=0.59). Secondary: There was no significant difference between the treatments in aortic-valve-related events (HR, 0.97; 95% CI, 0.83 to 1.14; P=0.73). Aortic-valve replacement occurred in 28.3% of patients in the simvastatin plus ezetimibe group and in 29.9% of patients in the placebo group (HR, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Ischemic cardiovascular events occurred in 15.7% of patients in the simvastatin plus ezetimibe group compared to 20.1% of patients in the placebo group (HR, 0.78; 95% CI, 0.63 to 0.97; P=0.02). A total of 7.3% of patients in the simvastatin plus ezetimibe group required CABG compared to 10.8% of patients in the placebo group (HR, 0.68; 95% CI, 0.50 to 0.93; P=0.02). There was no significant difference in the progression of aortic stenosis between the treatment groups. The mean peak aortic jet velocity was 3.71 m per second in the placebo group compared to 3.69 m per second in the simvastatin plus ezetimibe group at the end of the study (95% CI, -0.06 to 0.05; P=0.83). The mean pressure gradient increased to 34.4 mm Hg in the placebo group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to 34.0±15.1 mm Hg in the simvastatin plus ezetimibe group at the end of the study. There was no significant difference in the aortic-valve area between the treatment groups. There was no significant difference in overall mortality among the treatment groups (P=0.80). The composite outcome of death from cardiovascular causes and the individual components of this composite outcome did not differ significantly between the two groups (P=0.34). There was a significant increase in the number of patients with elevated liver enzyme levels in the simvastatin plus ezetimibe group. There was also a higher incidence of cancer in the simvastatin plus ezetimibe group (11.1%) compared to placebo (7.5%; P=0.01).
Sampalis et al.[99] (2007) Ezetimibe 10 mg/day vs placebo All patients received statin therapy.	Post-hoc analysis Adult patients with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals on statin therapy	N=825 6 weeks	Primary: Reduction in the 10-year risk of CAD after six weeks Secondary: Not reported	Primary: The addition of ezetimibe to ongoing statin therapy was associated with a 25.3% reduction in the 10-year risk of CAD (P<0.001). Secondary: Not reported
Cannon et al.[100] (2015) Ezetimibe 10 mg (simvastatin–ezetimibe group) vs placebo (simvastatin-	DB, RCT Patients ≥50 years of age who had been hospitalized within the preceding 10 days for an acute coronary syndrome (an acute myocardial infarction, with or without ST-segment elevation on	N=18,144 ≥2.5 years (median of 6 years)	Primary: Composite of death from cardiovascular disease, a major coronary event (nonfatal MI, documented unstable angina requiring hospital admission, or	Primary: Kaplan–Meier event rates for the primary end point at seven years were 32.7% in the simvastatin–ezetimibe group and 34.7% in the simvastatin-monotherapy group (absolute risk reduction, 2.0 percentage points; HR, 0.936; 95% CI, 0.89 to 0.99; P=0.016). Secondary: A composite of death from any cause, major coronary event, or nonfatal stroke: HR, 0.95; 95% CI, 0.90 to 1.0; P=0.03 A composite of death from coronary heart disease, nonfatal MI, or urgent

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
monotherapy group) All patients received simvastatin 40 mg	electrocardiography, or high-risk unstable angina) who had LDL-C >50 mg/dL		coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke Secondary: A composite of death from any cause, major coronary event, or nonfatal stroke; a composite of death from coronary heart disease, nonfatal MI, or urgent coronary revascularization ≥30 days after randomization; and a composite of death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days after randomization, or nonfatal stroke	coronary revascularization ≥30 days after randomization: HR, 0.91; 95% CI, 0.85 to 0.98; P=0.02 A composite of death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days after randomization, or nonfatal stroke: HR, 0.95; 95% CI, 0.90 to 1.0; P=0.04
Fleg et al.[101] (2008) SANDS Ezetimibe 10 mg	Subgroup analysis OL, RCT American Indian men and women ≥40 years	N=427 3 years	Primary: CIMT after 36 months of treatment	Primary: After 36 months, CIMT progressed in the standard group and regressed in the aggressive subgroups (ezetimibe plus statin and placebo; P<0.001 vs the standard group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs placebo All patients received aggressive statin therapy. Patients in the standard treatment arm served as the control group for this post-hoc analysis.	of age with type 2 diabetes, LDL-C >100 mg/dL, SBP >130 mm Hg, and no prior cardiovascular events; this trial examined the effects of aggressive goals for LDL-C (<70 mg/dl), non-HDL-C (<100 mg/dL), and BP (<115/75 mm Hg) reduction vs standard goals of <100 mg/dL, <130 mg/dL, and <130/80 mm Hg, respectively.		Secondary: Not reported	There was a similar percent of patients in the aggressive treatment arms who demonstrated no change or a decrease in CIMT with ezetimibe plus statin compared to placebo (62 vs 61%, respectively). Only 39% of patients in the standard arm demonstrated no change or a decrease in CIMT (P<0.0001 vs the aggressive arm). Cardiovascular events occurred in 3.5, 5.8, and 3.3% of patients in the standard, aggressive with ezetimibe plus statin, and aggressive statin monotherapy subgroups (placebo), respectively (P=0.62). Secondary: Not reported
Taylor et al.[102] (2009) Ezetimibe 10 mg QD vs niacin SR (Niaspan®) 2 g (titrated) QD	OL, PG, RCT Patients ≥30 years of age with atherosclerotic coronary or vascular disease or a CHD risk equivalent (diabetes mellitus, 10-year Framingham risk score ≥20%, coronary calcium score >200 for women or >400 for men who were receiving treatment with a statin (LDL-C <100 mg/dL and HDL-C <50 mg/dL for men or <55 mg/dL for	N=208 14 months	Primary: Change in CIMT after 14 months Secondary: Change in lipid values, composite of major adverse cardiovascular events (MI, myocardial revascularization, admission to the hospital for an acute coronary syndrome, and death from CHD), discontinuation of study drug due to	Primary: Treatment with niacin led to a significant reduction in mean and maximal CIMT at eight months (P=0.001 and P=0.004, respectively) and 14 months (P=0.001 and P<0.001, respectively). There was no significant change in mean or maximal CIMT with ezetimibe at eight or 14 months compared to baseline. There was a significant difference between the niacin group and the ezetimibe group (P=0.003). Secondary: The change in LDL-C in the ezetimibe group was -17.6 mg/dL compared to -10.0 mg/dL in the niacin group (P=0.01). The change in HDL-C in the ezetimibe group was -2.8 mg/dL compared to 7.5 mg/dL in the niacin group (P<0.001). There were significant reductions in TG in both groups. Major adverse cardiovascular events occurred in 5% of patients receiving ezetimibe compared to 1% of patients receiving niacin (P=0.04). Adverse drug effects led to withdrawal from the study in three of nine patients receiving ezetimibe and 17 of 27 patients receiving niacin (P=0.12).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	women)		adverse effects, health-related quality of life	There was no significant difference between the two groups in the quality of life at baseline or at 14 months.
Pauriah et al.[103] (2014) Simvastatin monotherapy vs high-potency statin group (patients who started on simvastatin and switched to atorvastatin or rosuvastatin vs ezetimibe/statin combination group	OS, RETRO Patients who had survived 30 days after their first acute MI, had not received prior statin or ezetimibe therapy, and were started on a statin within 30 days of acute MI	N=9,597 Mean follow-up of 3.2 years	Primary: Mortality, lipid levels Secondary: Not reported	Primary: The adjusted HR for the high-potency statin group was 0.72 (95% CI, 0.59 to 0.88; P<0.001), and for the ezetimibe/statin combination group, the adjusted HR was 0.96 (95% CI, 0.64 to 1.43; P<0.85). In the subgroup analysis of 2787 patients with complete data for GFR, cholesterol, and blood pressure, the HR for ezetimibe use and high-potency statin use were 1.03 (95% CI, 0.47 to 2.23; P=0.943) and 0.79 (95% CI, 0.55 to 1.131; P=0.19), respectively. There was a decrease in total cholesterol and LDL-C in all three groups with significantly greater percentage decrease in these measures in the high-potency statin group and the ezetimibe/statin combination group compared with the simvastatin monotherapy group. Because of higher baseline total cholesterol levels, the best achieved total cholesterol levels were not lower in the high-potency statin and ezetimibe/statin combination groups. Secondary: Not reported
Meaney et al.[104] (2009) VYCTOR Pravastatin 40 mg QD (ezetimibe 10 mg/day could be added if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions)	RCT, OL Patients 40 to 72 years of age with a 10-year absolute risk for coronary death or myocardial infarction ≥20 according to the ATP III recommendations	N=90 1 year	Primary: Change in CIMT Secondary: Changes in LDL-C and hsCRP	Primary: After one year, CIMT values were 0.93mm (-30%; P<0.01 vs baseline), 0.90 mm (-30%; P<0.01 vs baseline), and 0.92 mm (-25%; P<0.01 vs baseline) for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively. There was no significant difference among the treatment groups. Secondary: At the end of the study, LDL-C levels were 48, 45, and 48 mg/dL for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively (P<0.01 vs baseline for all). There was no significant difference among the treatment groups. The proportion of diabetic patients who attained LDL-C <70 mg/dL at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin 40 mg QD (dose could be increased to 80 mg/day if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions) vs simvastatin-ezetimibe 20-10 mg QD (dose of simvastatin could be increased to 40 mg/day if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions)				end of the trial were 62, 80, and 78% for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively (P values not significant). There was no significant difference among the treatment groups. There were no significant differences in hsCRP, HDL-C, TG among the treatment groups.

Drug regimen abbreviations: QD=once-daily, SR=sustained-release, XR=extended-release
Study abbreviations: AC=active comparator, DB=double=blind, DD=double dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open label, OR=odds ratio, OS= observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, SB=single-blind, XO=cross-over
Miscellaneous abbreviations: apo=apolipoprotein, ALT=alanine aminotransferase, AST=aspartate aminotransferase, AVD=atherosclerotic vascular disease, BP=blood pressure, BMI=body mass index, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, CIMT=carotid intima-media thickness, CK=creatine kinase, CRP=C-reactive protein, FPG=fasting plasma glucose, HAART=highly active antiretroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, heFH=heterozygous familial hypercholesterolemia, HIV=human immunodeficiency virus, HR=hazard ratio, hoFH=homozygous familial hypercholesterolemia, hsCRP=high-sensitivity C-reactive protein, IDL-C=intermediate-density lipoprotein cholesterol, IMT=intima-media thickness, JBS2=Joint British Society 2, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MDA-LDL= malondialdehydemodified LDL, MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, PCI=percutaneous intervention, RLP-C=remnant-like particle cholesterol, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, US=United States, 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 9. Relative Cost of the Cholesterol Absorption Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ezetimibe	tablet	Zetia®*	$$$$$	$

N/A=Not available.

X. Conclusions

Ezetimibe is the only cholesterol absorption inhibitor in this class and it is available in a generic formulation. It is approved for the treatment of primary hypercholesterolemia, mixed hyperlipidemia, homozygous familial hypercholesterolemia, and homozygous familial sitosterolemia.[1]

In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When low-density lipoprotein lowering is required, initial treatment with a statin, a bile acid sequestrant, or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing low-density lipoprotein cholesterol (LDL-C) levels and are recommended in patients with established coronary heart disease or coronary heart disease equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy. With regards to the specific use of ezetimibe in lipid management, treatment guidelines recognize ezetimibe as a potential option to be added to statin therapy if lipid goals have not been met, or as a potential treatment option in

patients who are unable to take statins, bile acid sequestrants, and/or niacin. Of note, the long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown.[2-8]

The American College of Cardiology/American Heart Association released updated guidelines in 2013 which support initiating a statin in patients with established atherosclerotic cardiovascular disease (ASCVD). According to these recommendations, percent reduction in LDL-C is an indicator of response and adherence to therapy, but treating to a targeted level is not a primary goal.[7] Combination therapy can be considered on an individual basis, but studies of combination therapy have generally not shown benefit beyond statin monotherapy. Additionally, if patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.[7] The 2018 American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol recommend using an LDL-C threshold of 70 mg/dL to consider the addition of non-statins to statin therapy in very high-risk ASCVD patients.[6]

Clinical trials have demonstrated that monotherapy with ezetimibe significantly lowers total cholesterol, LDL-C, apolipoprotein B, and triglycerides, as well as increases high-density lipoprotein cholesterol compared to placebo.[1,28-32] The majority of available clinical trials evaluate ezetimibe as combination therapy with colesevelam, fenofibrates, niacin, and statins, and results demonstrate that complementary effects on various lipid/lipoprotein parameters are achieved.[18-26,33-87,97-104] Recent clinical trials comparing ezetimibe with proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors demonstrate greater reductions in LDL-C with the PCSK9 inhibitors; however, data on the extent of benefit on cardiovascular morbidity and mortality is limited, or has not been determined.[88-96] The effects of ezetimibe given either alone or in addition to a statin or fenofibrate on cardiovascular morbidity and mortality have not been established.[1]

Therefore, all brand cholesterol absorption inhibitors 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 cholesterol absorption 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Fibric Acid Derivatives
AHFS Class 240606
February 7, 2024

I. Overview

The antilipemic agents are categorized into six different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, HMG-CoA reductase inhibitors (statins), and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPARα). Activation of PPARα increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of Apo CIII. The resulting decrease in triglycerides (TG) produces an alteration in the size and composition of low-density lipoprotein cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of high-density lipoprotein cholesterol (HDL-C), as well as apo AI and AII.[1-8] The fibric acid derivatives can decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They also lower LDL-C by 5 to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.[9]

There are several fenofibrate products that are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose. Fenofibric acid is the active metabolite of fenofibrate.[10,11] All products are available in a generic formulation.

The fibric acid derivatives that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. This class was last reviewed in February 2022.

Table 1. Fibric Acid Derivatives Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Fenofibrate	capsule, tablet	Fenoglide®*, Lipofen®*	fenofibrate
Fenofibrate, micronized	capsule*	Antara®*	fenofibrate, micronized
Fenofibrate, nanocrystallized	tablet	Tricor®*	fenofibrate, nanocrystallized
Fenofibric acid	delayed-release capsule, tablet	Trilipix®*	fenofibric acid
Gemfibrozil	tablet	Lopid®*	gemfibrozil

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the fibric acid derivatives are summarized in Table 2.

Table 2. Treatment Guidelines Using the Fibric Acid Derivatives

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C

Clinical Guideline	Recommendation
Education Program Adult Treatment Panel III Guidelines (2004)[12]	levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood**	<u>General recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made.

Clinical Guideline	Recommendation
Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)[9]	• Initiate LDL lowering drug therapy with a statin, bile acid sequestrant, or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Statins</u> • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. <u>Bile acid sequestrants</u> • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. <u>Nicotinic acid</u> • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout, and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <u>Fibric acid derivatives (fibrates)</u> • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <u>Omega-3 fatty acids</u> • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3

Clinical Guideline	Recommendation
	fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2017)[13] and Executive Summary (2020)[14]**	<u>Cholesterol Goals</u> • For patients at low risk for ASCVD (i.e., no risk factors), goals of LDL-C<130 mg/dL, non-HDL-C<160 mg/dL, and TG<150 mg/dL are recommended. • For patients at moderate risk for ASCVD (i.e., two or fewer risk factors and a calculated 10-year risk of <10%), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at high risk for ASCVD (i.e., two or more risk factors and a 10-year risk between 10% and 20% or who have diabetes or stage ≥3 CKD with no other risk factors), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at very high risk for ASCVD (i.e., established clinical ASCVD or recent hospitalization for ACS, carotid or peripheral vascular disease, or 10-year risk >20%; diabetes with one or more risk factor(s); CKD stage 3 or higher with albuminuria; or HeFH), goals of LDL-C<70 mg/dL, non-HDL-C<100 mg/dL, apo B<80 mg/dL, and TG<150 mg/dL are recommended. • For individuals at extreme risk (i.e., progressive ASCVD including unstable angina that persists after achieving an LDL-C <70 mg/dL; established clinical ASCVD in individuals with diabetes, CKD stage 3 or higher, and/or HeFH); history of premature ASCVD (<55 years of age for males or <65 years of age for females), goals of LDL-C<55 mg/dL, non-HDL-C<80 mg/dL, apo B<70 mg/dL, and TG<150 mg/dL are recommended. • An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100 to 129 mg/dL considered "borderline" and 130 mg/dL or greater considered "high" (based on recommendations from the American Academy of Pediatrics). • Due to its potential cardioprotective role, HDL-C should be >40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C. <u>General Recommendations</u> • A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes and patient education with pharmacotherapy as needed to achieve evidence based targets. • A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include ≥30 minutes of moderate-intensity physical activity [consuming 4 to 7 kcal/min] four to six times weekly, with an expenditure of ≥200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities. • Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs. • In addition to aerobic activity, muscle-strengthening activity is recommended at least two days a week.

Clinical Guideline	Recommendation
	• For adults, a reduced-calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains (primarily whole grains), fish, and lean meats is recommended. • For adults, the intake of saturated fats, trans-fats, and cholesterol should be limited, while LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10 to 25 g/day). • Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children. • Excessive alcohol intake should be avoided. • Tobacco cessation should be strongly encouraged and facilitated. • In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals. <u>Statins</u> • Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. • For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction. • In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered. • Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, who also have at least one additional risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL. • Extreme risk individuals should be treated with statins to target an even lower LDL-C treatment goal of <55 mg/dL. <u>Fibrates</u> • Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). • Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add fibrate. • In patients treated with a statin and icosapent ethyl with TG≥150 mg/dL, a fibrate may be considered. <u>Omega-3 Fish Oil</u> • Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose. • Omega-3 should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add omega-3. <u>Niacin</u> • Niacin therapy is recommended principally as an adjunct for reducing TG. • Niacin therapy should not be used in individuals aggressively treated with statin due to absence of additional benefits with well-controlled LDL-C.

Clinical Guideline	Recommendation

	• Niacin should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin.
	• In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add niacin.
	• In patients treated with a statin and icosapent ethyl with TG>150 mg/dL, niacin may be considered.
	
	<u>Icosapent Ethyl</u>
	• Icosapent ethyl (two grams twice daily) should be added to a statin in any patient with established ASCVD or diabetes with two or more ASCVD risk factors and triglycerides between 135 to 499 mg/dL to prevent ASCVD events.
	
	<u>Bile Acid Sequestrants</u>
	• Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG.
	
	<u>Cholesterol Absorption Inhibitors</u>
	• Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals.
	• Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk.
	
	<u>PCSK9 Inhibitors</u>
	• Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.
	• PCSK9 inhibitors should be considered in patients with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.
	
	<u>Combination Therapy</u>
	• Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal.
	
	<u>Special Considerations: Women</u>
	• Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient.
	• Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended.
	
	<u>Special Considerations: Children and Adolescents</u>
	• Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, and particularly for those satisfying the following criteria:
	  o LDL-C ≥190 mg/dL
	  o LDL-C ≥160 mg/dL and the presence of two or more cardiovascular risk factors, even after vigorous intervention
	  o Family history of premature ASCVD (before 55 years of age), or
	  o Having overweight, obesity, or other elements of the insulin resistance syndrome
	
	<u>Follow-up and Monitoring</u>

Clinical Guideline	Recommendation
	• Reassess individuals' lipid status six weeks after therapy initiation and again at six-week intervals until the treatment goal is achieved. • While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals. • While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment. • More frequent lipid status evaluation is recommended in situations such as deterioration of diabetes control, use of a new drug known to affect lipid levels, progression of atherothrombotic disease, considerable weight gain, unexpected adverse change in any lipid parameter, development of a new ASCVD risk factor, or convincing new clinical trial evidence or guidelines that suggest stricter lipid goals. • Liver transaminase levels should be measured before and three months after niacin or fibric acid treatment initiation because most liver abnormalities occur within 3 months of treatment initiation. Liver transaminase levels should be measured periodically thereafter (e.g., semiannually or annually). • Creatine kinase levels should be assessed and the statin discontinued, at least temporarily, when an individual reports clinically significant myalgias or muscle weakness on statin therapy.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (2018)**[15]	<u>Top 10 messages to reduce risk of atherosclerotic cardiovascular disease through cholesterol management</u> • In all individuals, emphasize a heart-healthy lifestyle across the life course. • In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. ○ Clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin. • In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy. Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. • In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. • In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. • In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 to 189 mg/dL (≥1.8 to 4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium (CAC).

Clinical Guideline	Recommendation
	• Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement four to 12 weeks after statin initiation or dose adjustment, repeated every three to 12 months as needed. <u>Recommendations for Statin Therapy Use in Patients With ASCVD</u> • In patients who are 75 years of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. • In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels. • In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe. • In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost. • In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy. • In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences. • In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. • In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe. • In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (three to five years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events. <u>Recommendations for primary severe hypercholesterolemia (LDL-C ≥190 mg/dL)</u> • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher, maximally tolerated statin therapy is recommended. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher, ezetimibe therapy is reasonable. • In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL, who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL, while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered. • In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. • In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or

Clinical Guideline	Recommendation
	higher and who achieve an on-treatment LDL-C level of 130 mg/dL or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. Recommendations for patients with diabetes mellitus • In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. Primary prevention recommendations for adults 40 to 75 years of age with LDL levels 70 to 189 mg/dL • In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more. • For the primary prevention of clinical ASCVD in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL, the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%). • Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision. • In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy. • In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND o If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); o If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥ 55 years of age; o If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy • In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin. • In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. Recommendations for older adults • In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL, initiating a moderate-intensity statin may be reasonable. • In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy. • In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL, it may

Clinical Guideline	Recommendation
	be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy. <u>Recommendations for children and adolescents</u> • In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity. • In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C. • In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL or higher with a clinical presentation consistent with familial hypercholesterolemia (FH) and who do not respond adequately with three to six months of lifestyle therapy, it is reasonable to initiate statin therapy. • In children and adolescents with a family history of either early CVD or significant hypercholesterolemia, it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age two years to detect FH or rare forms of hypercholesterolemia. • In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia. • In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome. • In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of nine and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities. <u>Recommendations for hypertriglyceridemia</u> • In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides. • In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy. • In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy. • In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL, and especially fasting triglycerides ≥1000 mg/dL), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy. <u>Recommendations for statin safety and statin-associated side effects</u>

Clinical Guideline	Recommendation
	• A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully. • In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors. • In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and SAMS, is recommended before initiation of treatment. • In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy. • In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss. • In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity. • In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks. • In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit. • Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS. • In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)[16]**	<u>Statin treatment</u> • The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin

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	therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. • For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%. • Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. • Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. • Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal.

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	○ Patient characteristics or concomitant use of drugs affecting statin metabolism. ○ >75 years of age. • Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: ○ History of hemorrhagic stroke. ○ Asian ancestry. • Creatine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). • Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug). • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: ○ To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. ○ If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: ○ Discontinue the statin until the symptoms can be evaluated. ○ Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).

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	○ If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. ○ If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. ○ Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. ○ If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. ○ If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: ○ Reinforce medication adherence. ○ Reinforce adherence to intensive lifestyle changes. ○ Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: ○ High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; ○ Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; ○ LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: ○ Individuals with clinical ASCVD <75 years of age. ○ Individuals with baseline LDL-C ≥190 mg/dL. ○ Individuals 40 to 75 years of age with diabetes mellitus. ○ Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. • In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-

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	reduction benefits outweigh the potential for adverse effects. Non statin safety • Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. • Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. • In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. • To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. • Bile acid sequestrants should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. • A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. • It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. • It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. • Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. • Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. • Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day.

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	• If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)**[17]	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy

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	along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for

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	primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. Recommendations for treatment of tobacco use • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. Recommendations for aspirin use • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2021)**[18]	Drugs • Currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins), fibrates, bile acid sequestrants, selective cholesterol absorption inhibitors (e.g. ezetimibe) and, more recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and bempedoic acid. Response to all therapy varies widely among individuals and therefore monitoring the effect on LDL-C levels is recommended. • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins also lower triglycerides, and may reduce pancreatitis risk. • Statins should be used as the drugs of first choice in patients at increased risk of ASCVD. • Selective cholesterol absorption inhibitors (ezetimibe) should be considered as second-line therapy, either on top of statins when the therapeutic goal is not achieved, or when a statin cannot be prescribed. • Among patients in whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C levels when administered in combination with ezetimibe.

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	• PCSK9 inhibitors also lower triglycerides, raise HDL-C and apolipoprotein A-I, and lower lipoprotein(a), although the relative contributions of these lipid modifications remain unknown. • PCSK9 inhibitors decrease LDL-C by up to 60%, either as monotherapy or in addition to the maximal statin dose or other lipid-lowering therapies (ezetimibe). • Fibrates are used primarily for triglyceride lowering and, occasionally, for increasing HDL-C. Evidence supporting the use of these drugs for CVD event reduction is limited and, given the strong evidence favoring statins, routine use of these drugs in CVD prevention is not recommended. In order to prevent pancreatitis, when triglycerides are >10 mmol/L (>900 mg/dL) they must be reduced not only by drugs but also by restriction of alcohol, treatment of DM, withdrawal of estrogen therapy, etc. In those rare patients with severe primary hypertriglyceridemia, specialist referral must be considered. <u>Recommendations for pharmacological low-density lipoprotein cholesterol lowering for those <70 years of age</u> • It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group. • If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. • For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered. • For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may be considered. • If the goal is not achieved, statin combination with a bile acid sequestrant may be considered.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2021)**[19]	<u>Secondary Stroke Prevention</u> • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or transient ischemic attack (TIA) presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other clinical ASCVD. • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, and LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD. • Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2018 ACC/AHA cholesterol guidelines, which include lifestyle modifications, dietary recommendations, and medication recommendations. <u>Treatment of Hypertriglyceridemia</u> • In patients with ischemic stroke or TIA with fasting TG 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL, on moderate or high-intensity statin, with HbA_{1c}

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	<10%, and with no history of pancreatitis, AF, or severe heart failure, treatment with icosapent ethyl (IPE) 2 g twice a day is reasonable to reduce risk of recurrent stroke. • To further reduce the risk of ASCVD in patients with severe hypertriglyceridemia (>500 mg/dL), patients should implement a low-fat diet, avoid refined carbohydrates and alcohol, and consume omega-3 fatty acids.
American Association of the Study of Liver Disease: **Primary Biliary Cholangitis (2018)[20] and Update (2021)[21]**	• Ursodeoxycholic acid (UDCA) at a dose of 13 to 15 mg/kg/day is the first-line therapy for primary biliary cholangitis (PBC). • UDCA is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage. • For patients requiring bile acid sequestrants, UDCA should be given at least one hour before or four hours after the bile acid sequestrant. • Biochemical response to UDCA should be evaluated at 12 months after treatment initiation to determine whether patients should be considered for second-line therapy. • Obeticholic acid (OCA) was approved by the Food and Drug Administration in May 2016 to be used in combination with UDCA in patients with PBC who have inadequate response to at least one year of treatment with UDCA, or as monotherapy for those patients who are intolerant to UDCA. • Patients who are inadequate responders to UDCA should be considered for treatment with OCA, starting at 5 mg/day. • Fibrates can be considered as off-label alternatives for patients with PBC and inadequate response to UDCA, although fibrates are discouraged in patients with decompensated liver disease. • Use of OCA and fibrates is discouraged in patients with decompensated liver disease (Child-Pugh-Turcotte B or C). • OCA is contraindicated in patients with advanced cirrhosis, defined as cirrhosis with current or prior evidence of liver decompensation or portal hypertension. • Cholestyramine, colestipol, and colesevelam are nonabsorbable, highly positively charged resins that bind to negatively charged anions such as bile acids. It is not known which substance in the gut they may be binding to that leads to improved cholestatic itching, and clinical trials proving their efficacy are limited, but they have a long track record of clinical use.
National Institute for Health and Clinical Excellence: **Identification and management of familial hypercholesterolaemia (2008)[22]** **Last updated October 2019**	<u>Drug treatment in adults</u> • When offering lipid-modifying drug therapy to adults with familial hypercholesterolemia (FH), inform the patient that this treatment should be life-long. • Offer a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications or intolerance to initial statin therapy. • Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who have been initiated on statin therapy when: o Serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy AND o Consideration is being given to changing from initial statin therapy to an alternative statin. • Appropriate control of cholesterol concentrations should be based on

Clinical Guideline	Recommendation
	individualized risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. • Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist center. • Offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). • Offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are at a very high risk of a coronary event [i.e., they have established coronary heart disease, a family history of premature coronary heart disease, or two or more other cardiovascular risk factors (e.g. they are male, they smoke, or they have hypertension or diabetes)]. • Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration. • The decision to offer treatment with a bile acid sequestrant (resin) or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH. • Exercise caution when adding a fibrate to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together. <u>Drug treatment in children and young people</u> • All children and young people diagnosed with, or being investigated for, a diagnosis of FH should have a referral to a specialist with expertise in FH in children and young people. • Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of ten years. The decision to defer or offer lipid-modifying drug therapy to a child or young person should take into account their age, the age of onset of coronary heart disease within the family, and the presence of other cardiovascular risk factors, including LCL-C concentration. • When offering lipid-modifying drug therapy for children or young people, inform the child/young person and their parent/caregiver that this treatment should be life-long. • Offer statins to children with FH by the age of ten years or at the earliest opportunity thereafter. • For children and young people with FH, consider a statin that is licensed for use in the appropriate age group. • Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group. • In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering: o A higher dose of statin than is licensed for use in the age group, and/or o More than one lipid-modifying drug therapy, and/or o Lipid-modifying drug therapy before the age of ten years. • In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy, and this should be considered before LDL apheresis. • In children and young people with FH who are intolerant of statins, consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration [such as bile acid sequestrants (resins), fibrates, or ezetimibe].

Clinical Guideline	Recommendation
	• Routine monitoring of growth and pubertal development in children and young people with FH is recommended.
American College of Cardiology: **Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2022)**[23]	• Provides recommendations for situations not covered by the 2018 ACC/AHA cholesterol guidelines and for whether or when to use non-statin therapies if response to statins is deemed inadequate. • For all patient groups, lifestyle modification (adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) is a critical component of ASCVD risk reduction. The clinician-patient discussion regarding the addition of a non-statin medication to the current medication regimen should address the potential for net ASCVD risk reduction, safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering, cost, convenience, and medication storage, pill burden, frequency and route of administration, potential to jeopardize adherence to evidence-based therapies and patient preference. <u>Adults With Clinical ASCVD on Statin Therapy for Secondary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider LDL apheresis under care of lipid specialist if baseline LDL-C ≥190 mg/dL not due to secondary causes without clinical or genetic diagnosis of familial hypercholesterolemia. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH under care of lipid specialist, if at very high risk and baseline LDL-C ≥190 mg/dL not due to secondary causes with clinical diagnosis or genetic confirmation of familial hypercholesterolemia. <u>Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Primary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH.
European Atherosclerosis Society/European Society of Vascular Medicine Joint Statement: **Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease (2021)**[24]	• Statins, at the highest tolerated dose, are indicated in patients with PAD for the prevention of cardiovascular events. • LCL-C should be lowered to <1.4 mmol/L and by >50% if pre-treatment values are 1.8 to 3.5 mmol/L. • Combination treatment with a statin and ezetimibe may be considered to improve LDL-C goal attainment. This approach could allow better tolerance of a lower dose of statin in patients with statin side-effects. • A PCSK9 inhibitor should be added if LDL-C levels remain 50% higher than goal despite statin treatment, with or without ezetimibe. • Antiplatelet therapy is indicated to prevent further cardiovascular events. This should either be clopidogrel 75 mg/day or the combination of aspirin 100 mg/day and rivaroxaban. • Dual antiplatelet therapy should be given for at least one month after drug coated balloon angioplasty, and for three months after either drug eluting or covered stent implantation. • Combination therapy with aspirin and rivaroxaban should be considered for dual antiplatelet therapy post-intervention.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the fibric acid derivatives 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 Fibric Acid Derivatives[1-8]

Indication	Fenofibrate	Fenofibric Acid	Gemfibrozil
Hypertriglyceridemia			
Adjunct to diet for treatment of adult patients with hypertriglyceridemia	✔ (Lofibra®)		
Adjunct to diet for treatment of severe hypertriglyceridemia	✔ (Antara®, Fenoglide®, Lipofen®, Tricor®)	✔ *	
Adjunct to diet for treatment of adult patients with very high elevations of serum triglyceride (TG) levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them			✔ †
Primary Hypercholesterolemia and Mixed Dyslipidemia			
Adjunct to diet to reduce elevated low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), TG, and apolipoprotein B (apo B), and to increase high density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia	✔ ‡	✔	
Adjunct to diet to reduce the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL-C and raise HDL-C) and who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated TG			✔

*Fibricor®: TG ≥500 mg/dL.
†Patients who present such risk typically have serum triglycerides over 2,000 mg/dl and have elevations of very low-density lipoprotein cholesterol (VLDL)-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Patients who consistently have total serum or plasma TG below 1,000 mg/dL are unlikely to present a risk of pancreatitis. Gemfibrozil may be considered for those patients with triglyceride elevations between 1000 and 2000 mg/dl who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis.
‡Antara®: when response to diet and nonpharmacological interventions alone has been inadequate.

IV. Pharmacokinetics

The pharmacokinetic parameters of the fibric acid derivatives are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Fibric Acid Derivatives[11]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Fenofibrate	60 to 90	99	Liver (% not reported) Kidneys (% not reported)	Renal (60 to 93) Feces (5 to 25)	20 to 22

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Fenofibric acid	81	99	Conjugation with glucuronic acid (% not reported)	Renal (primary; % not reported)	20
Gemfibrozil	Well absorbed (% not reported)	99	Liver (extensive; % not reported)	Renal (70) Feces (6)	1.5

V. Drug Interactions

Major drug interactions with the fibric acid derivatives are listed in Table 5.

Table 5. Major Drug Interactions with the Fibric Acid Derivatives[11]

Generic Name(s)	Interaction	Mechanism
Fenofibrate, Fenofibric acid, Gemfibrozil	Statins	The mechanism of interaction is not known. Severe myopathy may occur if fenofibrate and statins are coadministered.
Fenofibrate, Fenofibric acid, Gemfibrozil	Colchicine	Concurrent use of colchicine and fibric acid derivatives may result in an increased risk of myopathy, including rhabdomyolysis.
Fenofibrate, Fenofibric acid	Anticoagulants	Fibric acid derivatives may potentiate the inhibition of vitamin K dependent clotting factor synthesis by anticoagulants. The hypoprothrombinemic effect of anticoagulants may be increased by fibric acid derivatives and bleeding may occur.
Gemfibrozil	Bexarotene	Concurrent use of bexarotene and gemfibrozil may result in increased plasma concentrations of bexarotene.
Gemfibrozil	Dabrafenib	Inhibition of dabrafenib metabolism (CYP2C8) by gemfibrozil may elevate dabrafenib plasma concentrations, increasing the pharmacologic effects and risk for adverse reactions.
Gemfibrozil	Dasabuvir	Concurrent use of dasabuvir and gemfibrozil may result in increased dasabuvir exposure.
Gemfibrozil	Eltrombopag	Concurrent use of eltrombopag and gemfibrozil may result in increased eltrombopag plasma concentrations.
Gemfibrozil	Enzalutamide	Concurrent use of enzalutamide and gemfibrozil may result in increased enzalutamide exposure.
Gemfibrozil	Ezetimibe	Concurrent use of ezetimibe and gemfibrozil may result in increased ezetimibe concentrations and an increased risk of cholelithiasis.
Gemfibrozil	Imatinib	Concurrent use of gemfibrozil and imatinib may result in increased imatinib trough level or reduced imatinib exposure.
Gemfibrozil	Repaglinide	Gemfibrozil may inhibit the metabolism of repaglinide, resulting in an increase in the plasma concentrations and the risk of severe and protracted hypoglycemia.

VI. Adverse Drug Events

The most common adverse drug events reported with the fibric acid derivatives are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Fibric Acid Derivatives[1-8,10]

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Cardiovascular			
Angina pectoris	✔	-	-
Arrhythmia	✔	-	-

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Atrial fibrillation	✔	-	1
Cardiovascular disorder	✔	-	-
Coronary artery disorder	✔	-	-
Edema	✔	-	-
Electrocardiogram abnormal	✔	-	-
Hypertension	✔	✔	-
Hypesthesia	-	-	✔
Hypotension	✔	-	-
Migraine	✔	-	-
Myocardial infarction	✔	-	-
Palpitation	✔	-	-
Peripheral edema	✔	-	-
Peripheral vascular disorder	✔	-	✔
Phlebitis	✔	-	-
Syncope	-	-	✔
Tachycardia	✔	-	-
Varicose vein	✔	-	-
Vascular disorder	✔	-	-
Vasodilatation	✔	-	-
Ventricular extrasystoles	✔	-	-
Central Nervous System			
Anxiety	✔	-	-
Confusion	-	-	✔
Convulsion	-	-	✔
Depression	✔	-	✔
Dizziness	✔	3 to 4	✔
Fatigue	-	2 to 3	4
Fever	✔	-	-
Headache	3	12 to 13	1
Hypertonia	✔	-	-
Insomnia	✔	✔	-
Libido decreased	✔	-	✔
Nervousness	✔	-	-
Neuralgia	✔	-	-
Paresthesia	✔	-	✔
Pain	✔	-	-
Peripheral neuritis	-	-	✔
Somnolence	✔	-	✔
Vertigo	✔	-	2
Dermatological			
Acne	✔	-	-
Alopecia	✔	-	-
Angioedema	-	-	✔
Contact dermatitis	✔	-	-
Eczema	✔	-	2
Exfoliative dermatitis	-	-	✔
Fungal dermatitis	✔	-	-
Herpes simplex	✔	-	-
Herpes zoster	✔	-	-
Nail disorder	✔	-	-
Maculopapular rash	✔	-	-
Photosensitivity reaction	✔	-	✔
Pruritus	✔	-	-
Rash	-	-	2

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Skin disorder	✔	-	-
Skin ulcer	✔	-	-
Stevens-Johnson syndrome	✔	✔	-
Sweating	✔	-	-
Toxic epidermal necrolysis	✔	✔	-
Urticaria	✔	-	✔
Vasculitis	-	-	✔
Endocrine and Metabolic			
Diabetes mellitus	✔	-	-
Gout	✔	-	-
Gynecomastia	✔	-	-
Hypoglycemia	✔	-	-
Hyperuricemia	✔	-	-
Gastrointestinal			
Abdominal pain	5	✔	10
Anorexia	✔	-	-
Cholestatic jaundice	-	-	✔
Colitis	✔	-	-
Constipation	2	3	1
Diarrhea	2	3 to 4	7
Duodenal ulcer	✔	3 to 5	-
Dyspepsia	✔	-	20
Eructation	✔	-	-
Esophagitis	✔	-	-
Flatulence	✔	-	-
Nausea	2	4 to 6	2
Peptic ulcer	✔	-	-
Vomiting	✔	-	2
Weight gain/loss	✔	-	-
Genitourinary			
Creatinine increased	✔	-	-
Cystitis	✔	-	-
Decreased male fertility	-	-	✔
Dysuria	✔	-	-
Impotence	-	-	✔
Kidney function abnormal	✔	-	✔
Nephrotoxicity	✔	✔	✔
Prostatic disorder	✔	-	-
Unintended pregnancy	✔	-	-
Urinary frequency	✔	-	-
Urinary tract infection	-	✔	-
Vaginal moniliasis	✔	-	-
Hematologic			
Agranulocytosis	✔	✔	-
Anemia	✔	✔	✔
Ecchymosis	✔	-	-
Eosinophilia	✔	-	-
Hematocrit decreased	-	✔	-
Hemoglobin decreased	-	✔	-
Leukopenia	✔	✔	✔
Lymphadenopathy	✔	-	-
Thrombocytopenia	✔	✔	✔
Hepatic			
Alkaline phosphokinase increased	-	-	✔

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
ALT increased	3	1 to 3	✔
AST increased	3	✔	✔
Bilirubin increased	-	-	✔
Cirrhosis	✔	✔	-
CPK increased	3	✔	✔
Hepatic enzymes increased	✔	✔	-
Hepatitis	✔	✔	-
Jaundice	-	-	✔
Liver fatty deposit	✔	-	-
Laboratory Test Abnormalities			
Serum creatinine increased	✔	✔	-
Musculoskeletal			
Arthralgia	✔	4	✔
Arthritis	✔	-	-
Arthrosis	✔	-	-
Bursitis	✔	-	-
Back pain	3	4 to 6	-
Joint disorder	✔	-	-
Leg cramps	✔	-	-
Muscle pain/spasm	✔	3 to 4	-
Myalgia	✔	3 to 4	-
Myasthenia	✔	-	✔
Myopathy	✔	-	✔
Myositis	✔	✔	-
Painful extremities	-	3 to 5	✔
Paresthesia	✔	-	✔
Rhabdomyolysis	✔	✔	✔
Synovitis	-	-	✔
Tenosynovitis	✔	-	-
Weakness	✔	✔	-
Respiratory			
Asthma	✔	-	-
Bronchitis	✔	✔	-
Cough	✔	✔	-
Dyspnea	✔	-	-
Laryngeal edema	-	-	✔
Laryngitis	✔	-	-
Nasopharyngitis	-	4 to 5	-
Pharyngitis	✔	-	-
Pneumonia	✔	-	-
Pulmonary embolism	✔	✔	-
Respiratory disorder	6	-	-
Rhinitis	2	-	-
Sinusitis	✔	3 to 4	-
Upper respiratory infection	-	4 to 5	-
Other			
Allergic reaction	✔	-	-
Amblyopia	✔	-	-
Anaphylaxis	-	-	✔
Appendicitis, acute	-	-	1
Asthenia	2	-	-
Blurred vision	-	-	✔
Cataracts	✔	-	✔
Chest pain	✔	-	-

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Cholecystitis	✔	-	✔
Cholelithiasis	✔	✔	✔
Conjunctivitis	✔	-	-
Cyst	✔	-	-
Deep vein thrombosis	✔	✔	-
Drug-induced lupus syndrome	-	-	✔
Dry mouth	✔	-	-
Ear pain	✔	-	-
Eye disorder	✔	-	-
Flu syndrome	2	-	-
Hernia	✔	-	-
Hypersensitivity reaction	✔	✔	-
Infection	✔	-	-
Influenza	-	✔	-
Intracerebral hemorrhage	-	-	✔
Malaise	✔	-	-
Otitis media	✔	-	-
Pancreatitis	✔	✔	✔
Pharyngolaryngeal pain	-	✔	-
Raynaud's phenomenon	-	-	✔
Refraction disorder	✔	-	-
Retinal edema	-	-	✔
Seizure	-	-	✔
Syncope	-	-	✔
Taste perversion	-	-	✔
Vision abnormalities	✔	-	-

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the fibric acid derivatives are listed in Table 7.

Table 7. Usual Dosing Regimens for the Fibric Acid Derivatives[1-8,10]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Fenofibrate	Hypertriglyceridemia: Capsule (Lofibra®): initial, 67 to 200 mg/day; maximum 200 mg/day Tablet (Lofibra®): initial, 54 to 160 mg/day; maximum, 160 mg/day Primary hypercholesterolemia or mixed hyperlipidemia: Capsule (Antara®): 90 mg/day Capsule (Lofibra®): initial, 200 mg/day; maximum 200 mg/day Capsule (Lipofen®): 150 mg/day Tablet (Fenoglide®): 120 mg/day Tablet (Lofibra®): initial, 160 mg/day	Safety and efficacy in pediatric patients have not been established.	Capsule: 30 mg (Antara®) 50 mg (Lipofen®) 67 mg (Lofibra®) 90 mg (Antara®) 134 mg (Lofibra®) 150 mg (Lipofen®) 200 mg (Lofibra®) Tablet: 40 mg (Fenoglide®) 48 mg (Tricor®) 50 mg (Lipofen®) 54 mg (Lofibra®) 120 mg (Fenoglide®) 145 mg (Tricor®) 160 mg (Lofibra®)

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet (Tricor®): initial, 145 mg once daily Severe hypertriglyceridemia: Capsule (Antara®): 30 to 90 mg/day Capsule (Lipofen®): 50 to 150 mg/day Tablet (Fenoglide®): 40 to 120 mg/day Tablet (Tricor®): initial, 48 to 145 mg once daily; maximum, 145 mg/day		
Fenofibric acid	Primary hypercholesterolemia or mixed hyperlipidemia: Tablet: 105 mg/day Severe hypertriglyceridemia: Delayed-release capsule: 45 to 135 mg once daily Tablet: 35 to 105 mg/day	Safety and efficacy in pediatric patients have not been established.	Delayed-release capsule: 45 mg (Trilipix®) 135 mg (Trilipix®) Tablet: 35 mg 105 mg
Gemfibrozil	Hypertriglyceridemia (very high elevations of serum triglyceride): Tablet: 600 mg twice daily 30 minutes before breakfast and dinner Primary hypercholesterolemia or mixed hyperlipidemia: Tablet: 600 mg twice daily 30 minutes before breakfast and dinner	Safety and efficacy in pediatric patients have not been established.	Tablet: 600 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the fibric acid derivatives are summarized in Table 8. The pharmacological effects of fenofibric acid have been extensively studied through oral administration of fenofibrate, which is converted in vivo to fenofibric acid.[2]

Table 8. Comparative Clinical Trials with the Fibric Acid Derivatives

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Rosenson et al.[25] (2007) Fenofibrate 160 mg QD vs placebo	DB, PC, RCT Patients with fasting hypertriglyceridemia (≥1.7 and <6.9 mmol/L) and 2 or more of the NCEP ATP III criteria for the metabolic syndrome	N=59 19 weeks	Primary: Fasting TG, postprandial TG, oxidative stress, inflammatory response Secondary: Not reported	Primary: Fenofibrate treatment lowered fasting TG (-46.1%; P<0.0001) and postprandial (area under the curve) TG (-45.4%; P<0.0001) due to significant reductions in postprandial levels of large (-40.8%; P<0.0001), medium (-49.5%; P<0.0001) and VLDL particles. The number of fasting total LDL particles was reduced in fenofibrate-treated patients (-19.0%; P=0.0033) primarily due to reductions in small LDL particles (-40.3%; P<0.0001); these treatment differences persisted postprandially. Fasting and postprandial oxidized fatty acids were reduced in fenofibrate-treated patients compared to placebo-administered patients (-15.3%; P=0.0013, and 31.0%; P<0.0001, respectively). Fenofibrate therapy lowered inflammatory markers as follows: fasting and postprandial soluble VCAM-1 decreased by -10.9% for fasting VCAM-1 (P=0.0005), and by -12.0% for postprandial VCAM-1 (P=0.0001); and fasting and postprandial soluble ICAM-1 decreased by -14.8% for fasting ICAM-1 (P<0.0001) and by -15.3% for postprandial ICAM-1 (P<0.0001). Reductions in VCAM-1 and ICAM-1 were correlated with reductions in fasting and postprandial large VLDL particles (P<0.0001) as well as postprandial oxidized fatty acids (P<0.0005). Secondary: Not reported
Davidson et al.[26] (2006) TRIMS Fenofibrate 130	DB, MC, PC, RCT Patients between the ages of 21 and 79 years, with fasting	N=146 8 weeks	Primary: Changes or percent changes from baseline to the end-of-treatment in	Primary: There was a significant change from baseline in the mean percent decrease of TG in the fenofibrate group (36.6%) compared to essentially no change in the placebo group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD vs placebo	TG levels ≥300 and <1,000 mg/dL, and ≥2 of 4 additional components of the metabolic syndrome as defined by the NCEP ATP III		fasting TG Secondary: Changes or percent changes from baseline in TC, LDL-C, HDL-C, the TC:HDL-C ratio, VLDL-C, non-HDL-C; apo AI, B, and C-III; and remnant lipoprotein cholesterol	Secondary: There was no significant difference in TC change between the fenofibrate treatment and the placebo groups (P=0.085). LDL-C increased by a mean of 15.0% in the fenofibrate group compared to 3.2% in the placebo group (P=0.006). HDL-C increased by a mean of 14.0% in the fenofibrate group compared to 0.8% for placebo (P<0.001). The ratio of TC to HDL-C decreased with fenofibrate compared to placebo (-14.2 vs 0.8%; P<0.001). VLDL-C declined by 33% with fenofibrate compared to a 1.6% decline with placebo treatment (P<0.001). Non-HDL-C decreased significantly more in the fenofibrate group (-7.5 vs -1.1%; P=0.009). There was no significant difference in the rise in apo AI among the fenofibrate group vs the placebo response (5.3 vs 2.0%; P=0.212). Apo B declined significantly with fenofibrate compared to placebo (P<0.001, respectively). Apo CIII was markedly reduced in the fenofibrate group (P<0.001 compared to placebo). A significant reduction in remnant lipoprotein cholesterol was observed with fenofibrate treatment (-35.1 vs 12.3%; P<0.001).
Jones et al.[27] (2010) Fenofibric acid 135 mg/day vs	DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 and <400 mg/dL, HDL-C <40 mg/dL in men and	N=543 12 weeks	Primary: Percentage changes from baseline in HDL-C and TG Secondary: Changes from	Primary: The addition of fenofibric acid resulted in a significantly greater mean percentage improvement in HDL-C (13.0 vs 4.2%; P<0.001) and TG (-57.3 vs -39.7%; P<0.001) compared to placebo. Secondary: The addition of fenofibric acid resulted in significantly greater effect on all secondary variables on non-HDL-C (P<0.001), apo B (P<0.001), apo AI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo All patients received atorvastatin 40 mg/day and ezetimibe 10 mg/day	<50 mg/dL in women and LDL-C ≥130 mg/dL)		baseline in apo AI, VLDL-C, apo CIII, non-HDL-C, apo B, hsCRP, LDL-C; proportion of patients achieving lipoprotein and apoprotein goals after 12 weeks of treatment; safety	(P=0.004), VLDL-C (P<0.001), apo CIII (P<0.001) and hsCRP (P<0.001) compared to placebo. The addition of fenofibric acid and placebo resulted in a >50% reduction in LDL-C (52.9 vs 52.0%; P value not reported), for final mean levels of 70.3 and 72.2 mg/dL. A numerically higher proportion of patients who added fenofibric acid achieved the LDL-C goal <100 mg/dL (92.7 vs 86.3%), the combined target of LDL-C <100 mg/dL and non-HDL-C <130 mg/dL (91.2 vs 84.0%) and the combined target of LDL-C <100 mg/dL, non-HDL-C <130 mg/dL and apo B <90 mg/dL (88.4 vs 80.8%) (P values not reported). Similar proportions of patients receiving both treatments achieved the LDL-C goal <70 mg/dL (55.0 vs 56.5%) and the combined target of LDL-C <70 mg/dL, non-HDL-C <100 mg/dL and apo B <80 mg/dL specified for high risk patients (53.4 vs 51.3%) (P values not reported). Both treatments were generally well tolerated. The percentages of patients discontinuing treatment were similar (9.6 vs 11.0%; P value not reported). The most common adverse events leading to discontinuations were myalgia and increases in ALT and/or AST. The treatments were similar in the incidence of adverse events experienced, treatment-related adverse events, serious adverse events and adverse events leading to withdrawal. The most commonly reported adverse events (≥3%) were muscle spasms, myalgia, arthralgia, fatigue, diarrhea, nausea, and headache.
Hogue et al.[28] (2008) Fenofibrate 200 mg QD vs atorvastatin 20 mg QD	RCT Patients with type 2 diabetes and hypertriglyceridemia	N=40 6 weeks	Primary: Lipids and TRL, inflammation and adhesion molecules Secondary: Not reported	Primary: Treatment with atorvastatin led to a significant decrease in plasma TC (-37.7%; P<0.0001), plasma TG (-37.6%, P<0.0001), plasma apo B (-43.2%, P<.0001), TRL-C (-44.1%, P<0.0001), TRL-TG (-36.9%, P<0.0001), TRL apo B (-13.8%, P=0.04), LDL-C (-43.0%, P<0.0001), LDL apo B (-42.7%, P<0.0001), and a significant increase in HDL-C (17.9%, P=0.001), and HDL apo A-I levels (10.3%, P=0.004). Treatment with fenofibrate led to a significant decrease in plasma C (-10.9%, P=0.0001), plasma TG (-41.4%, P=0.0002), plasma apo B (-9.9%, P=0.01), TRL-C (-52.8%, P<0.0001), TRL-TG (-46.3%, P=0.0002), and TRL apo B (-14.8%, P=0.02) and a significant increase in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				LDL-C (15.9%, P=0.04) and HDL-C (8.9%, P=0.05). There were significant differences in the percentage changes of plasma cholesterol, plasma apo B, LDL-C, and LDL apo B between the two treatment groups. There was no significant difference in the percentage in changes of plasma TG between the treatment groups. Treatment with atorvastatin significantly decreased plasma levels of CRP (-26.9%, P=0.004), soluble ICAM-1 (-5.4%, P=0.03), soluble VCAM-1 (-4.4%, P=0.008), soluble E-selectin (-5.7%, P=0.02), MMP-9 (-39.6%, P=0.04), soluble phospholipase A2 (-14.8%, P=0.04), and oxidized LDL (-38.4%, P<0.0001). Fenofibrate significantly decreased soluble E-selectin levels only (-6.0, P=0.04) and increased soluble phospholipase A2 levels (22.5%, P=0.004). Secondary: Not reported
Arca et al.[29] (2007) Fenofibrate 200 mg/day vs atorvastatin 10 mg/day, titrated up to 80 mg/day	OL, RCT Patients 30 to 75 years of age with diagnosis of familial combined hyperlipidemia with TC and/or TG levels ≥90th Italian population percentiles, and/or hyper-apobeta-lipoproteinemia	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A and endothelin-1 Secondary: Not reported	Primary: Atorvastatin was associated with a significant 9% reduction in TC compared to fenofibrate (95% CI, 3.0 to 15.1; P=0.004). Atorvastatin was associated with a significant 17% reduction in LDL-C compared to fenofibrate (95% CI, 8.0 to 26.1; P<0.001). Fenofibrate was associated with a significant 15.5% reduction in TG compared to atorvastatin (95% CI, 3.35 to 27.70; P=0.013). Fenofibrate was associated with a significant 14.2% increase in HDL-C compared to atorvastatin (95% CI, 3.8 to 24.6%; P=0.008). Fenofibrate was associated with a significant 5.2 and 22.0% increase in apo AI and apo AII compared to atorvastatin (P=0.044 and P<0.001, respectively). Fenofibrate was associated with a significant 16.7% reduction in endothelin-1 from baseline (P<0.05). Atorvastatin was not associated with

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				a significant change in endothelin-1 (P value not reported). Secondary: Not reported
Goldberg et al.[30] (2009) Fenofibric acid 135 mg QD plus atorvastatin 20 to 40 mg QD vs fenofibric acid 135 mg QD vs atorvastatin 20 to 40 mg QD	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 mg/dL, HDL-C <40 mg/dL for men and <50 mg/dL for women and LDL-C ≥130 mg/dL after lipid therapy washout)	N=613 12 weeks	Primary: Percent changes from baseline in TG, HDL-C and LDL-C Secondary: Percent changes from baseline in VLDL-C, TC, apo B and hsCRP; safety	Primary: Combination therapy (atorvastatin 20 mg) resulted in significantly greater improvements in TG (-45.6 vs -16.5%; P<0.001) and HDL-C (14.0 vs 6.3%; P=0.005) compared to atorvastatin 20 mg and LDL-C (-33.7 vs -3.4%; P<0.001) compared to fenofibric acid. Similarly, significantly greater improvements were observed with combination therapy (40 mg) in TG (-42.1 vs -23.2%; P<0.001) and HDL-C (12.6 vs 5.3%; P=0.010) compared to atorvastatin 40 mg and LDL-C (-35.4 vs -3.4%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (20 mg) resulted in significantly higher mean percentages of decrease in non-HDL-C compared to fenofibric acid (P=0.026) and in VLDL-C compared to atorvastatin 20 mg (P=0.046). Combination therapy (40 mg) also resulted in significantly higher mean percentage of decrease in non-HDL-C compared to fenofibric acid (P<0.001) and in VLDL-C compared to atorvastatin 40 mg (P<0.001). Improvements in other secondary variables were similar between combination therapy and atorvastatin (TC; P=0.688, apo B; P=0.688 and hsCRP; P=0.074).
Roth et al.[31] (2010) Rosuvastatin 5 mg/day vs fenofibric acid 135 mg/day vs	DB, MC, RCT Patients with fasting LDL-C ≥130 mg/dL, TG ≥150 mg/dL and HDL-C <40 mg/dL	N=760 12 weeks (plus a 30 day safety follow up period)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Changes from baseline in non-HDL-C, VLDL-C, apo B, hsCRP and	Primary: Combination therapy resulted in a significantly greater mean percent change in HDL-C (23.0 vs 12.4%; *P*<0.001) and TG (-43.0 vs -17.5%; *P*<0.001) compared to rosuvastatin, and resulted in significantly higher mean percent decrease in LDL-C compared to fenofibric acid (28.7 vs 4.1%; *P*<0.001). Secondary: Combination therapy resulted in significantly greater improvements in non-HDL-C compared to either monotherapy, and significantly greater improvements in apo B, hsCRP, VLDL-C and TC compared to rosuvastatin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosuvastatin 5 mg/day plus fenofibric acid 135 mg/day			TC; safety; proportion of patients achieving LDL-C (<100 mg/dL) and non-HDL-C (<130 mg/dL) goals	All treatments were generally well tolerated, with discontinuations due to adverse events being higher with combination therapy (8.3%) and fenofibric acid (7.5%) compared to rosuvastatin (4.4%). The most common adverse events leading to discontinuation were myalgia and muscle spasms and nausea, fatigue and ALT and AST increases. The overall incidence of treatment-emergent adverse events was similar across treatments (58.5 to 63.0%). No significant differences were observed between the combination therapy and either monotherapy in the incidence of any category of adverse events (muscle, hepatic and renal related). In patients with a 10 year CHD risk >20%, the LDL-C goal <100 mg/dL was achieved by 50.5% of patients receiving combination therapy and rosuvastatin; the non-HDL-C goal <130 mg/dL was achieved by 49.5% of patients receiving combination therapy compared to 33.3% of patients receiving rosuvastatin (*P*=0.03). Both LDL-C and non-HDL-C goals were achieved by 44.3 vs 32.3% (*P*=0.10).
Jones et al.[32] (2009) Fenofibric acid 135 mg QD and rosuvastatin (10 or 20 mg) QD vs fenofibric acid 135 mg QD vs rosuvastatin 10, 20, or 40 mg QD	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=1,445 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP	Primary: Combination therapy (rosuvastatin 10 and 20 mg) was associated with a significantly greater increase in HDL-C (10 mg: 20.3 vs 8.5%; P<0.001 and 20 mg: 19.0 vs 10.3%; P<0.001) and a significantly greater decrease in TG (10 mg: 47.1 vs 24.4%; P<0.001 and 20 mg: 42.9 vs 25.6%; P<0.001) compared to rosuvastatin (10 and 20 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (10 mg: 37.2 vs 6.5%; P<0.001 and 20 mg: 38.8 vs 6.5%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (rosuvastatin 10 mg) was associated with a significantly greater reduction in non-HDL-C compared to fenofibric acid or rosuvastatin (10 mg) (P<0.001). Combination therapy was also associated with significantly greater improvements in VLDL-C (P<0.001), apo B (P<0.001) and hsCRP (P=0.013) compared to rosuvastatin. Combination therapy (rosuvastatin 20 mg) significantly improved non-HDL-C compared to fenofibric acid (P<0.001) and was associated with a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significantly greater improvement in VLDL-C (P=0.038) and hsCRP (P=0.010) compared to rosuvastatin (20 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
Ferdinand et al.[33] (2012) Fenofibric acid 135 mg QD and rosuvastatin 10 mg QD for 12 weeks, followed by fenofibric acid 135 mg QD and rosuvastatin 20 mg QD for up to 52 weeks Outcomes were evaluated from the end of the initial 12 week period (baseline) up to 52 weeks of treatment.	Post-hoc analysis Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=187 1 year	Primary: Change in baseline LDL-C, HDL-C, non-HDL-C, apo B, TG, hsCRP; proportion of patients achieving individual and combined goals for LDL-C and non-HDL-C; safety Secondary: Not reported	Primary: Increasing rosuvastatin from 10 to 20 mg, in combination with fenofibric acid for up to 52 weeks, resulted in significant changes from baseline in LDL-C (-9.5%), non-HDL-C (-0.6%), apoB (-8.5%), and HDL-C (3.6%) (P≤0.005 for all). TG levels remained unchanged (0.8%; P=0.055) at week 52. A greater proportion of patients achieved risk-stratified lipid goals at week 52 compared to baseline for LDL-C (89 vs 84%; P=0.26), non-HDL-C (50 vs 25%; P value not reported), and both LDL-C and non-HDL-C (50 vs 19%; P value not reported). The incidences of muscle-, hepatic-, and renal-related adverse events and laboratory values were within the expected range for combination therapy. The most commonly reported treatment-emergent adverse events (>10%) were upper respiratory tract infection (14.4%), headache (13.9%), and back pain (10.7%)/ Treatment-emergent serious adverse events occurred in seven percent of patients, and one death (MI) occurred, none of which were deemed to be treatment-related. Secondary: Not reported
Mohiuddin et al.[34] (2009) Fenofibric acid 135 mg QD plus simvastatin 20 to 40 mg QD vs fenofibric acid 135 mg QD	AC, DB, MC Patients >18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, and LDL-C ≥130 mg/dL)	N=657 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C,	Primary: Combination therapy was associated with a significantly greater increase in HDL-C (20 mg: 17.8 vs 7.2%; P<0.001 and 40 mg: 18.9 vs 8.5%; P<0.001) and a significantly greater decrease in TG (20 mg: 37.4 vs 14.2%; P<0.001 and 40 mg: 42.7 vs 22.4%; P<0.001) compared to simvastatin (20 and 40 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (20 mg: 24.0 vs 4.0%; P<0.001 and 40 mg: 25.3 vs 4.0%; P<0.001) compared to fenofibric acid. Secondary:

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vs simvastatin 20 to 80 mg QD			VLDL-C, TC, apo B and hsCRP	Combination therapy (simvastatin 20 mg) was associated with a significantly greater decrease in non-HDL-C (P<0.001) compared to fenofibric acid and simvastatin (20 mg). Combination therapy (simvastatin 20 mg) was associated with significant improvements in VLDL-C (P<0.001), apo B (P<0.001) and hsCRP (P=0.013) compared to simvastatin (20 mg). Combination therapy (simvastatin 40 mg) significantly (P<0.001) improved non-HDL-C compared to fenofibric acid, and resulted in a significantly greater improvement in VLDL-C (P=0.005) compared to simvastatin (40 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
Derosa et al.[35] (2009) Fenofibrate 145 mg/day and simvastatin 40 mg/day vs fenofibrate 145 mg/day vs simvastatin 40 mg/day	DB, MC, RCT Caucasian patients ≥18 years of age with type 2 diabetes mellitus and combined dyslipidemia who had never been treated with lipid-lowering medications	N=241 12 months	Primary: Lipid and lipoprotein profiles at six and 12 months Secondary: Not reported	Primary: After six months of therapy, there was a significant reduction in TC and LDL-C with simvastatin and fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively). There was no significant change in the fenofibrate group. After 12 months of therapy, there was a significant decrease in TC and LDL-C in all treatment groups (P<0.05 for fenofibrate, P<0.01 for the simvastatin and P<0.001 for fenofibrate plus simvastatin). TC was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). LDL-C was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.01). After six months of therapy, there was a significant reduction in TG with fenofibrate and fenofibrate plus simvastatin (P<0.05, respectively). There was no significant change in the simvastatin group. After 12 months of therapy, there was a significant decrease in TG in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate plus simvastatin). TG was significantly lower with fenofibrate + simvastatin compared to fenofibrate (P<0.05) or simvastatin (P<0.01). After six months of therapy, there was a significant increase in HDL-C with fenofibrate and fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively). There was no change in the simvastatin group. After 12 months of therapy, there was a significant increase in HDL-C in all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate plus simvastatin). HDL-C was significantly higher with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). After six months of therapy, there was no significant change in apo A1 or apo B in any treatment group. After 12 months of therapy, there was a significant increase of apo A1 with fenofibrate plus simvastatin. There was no significant difference between the treatment groups. After 12 months of therapy, there was a significant decrease of apo B in all groups (P<0.05 for fenofibrate, P<0.05 for simvastatin and P<0.01 for fenofibrate plus simvastatin). There was no significant difference between the treatment groups. There were no significant differences in Lp(a) after six or 12 months of therapy in any of the treatment groups. After six months of therapy, there was a significant decrease in hsCRP with fenofibrate plus simvastatin (P<0.05), but not in the other groups. After 12 months of therapy, there was a significant decrease in hsCRP with simvastatin and with fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively), but not with fenofibrate. The hsCRP value was significantly lower with fenofibrate plus simvastatin compared to fenofibrate or simvastatin (P<0.05). Secondary: Not reported
May et al.[36] (2008) DIACOR Fenofibrate 160 mg and simvastatin 20 mg QD vs fenofibrate 160 mg	DB, PC, RCT Patients with type 2 diabetes, no CHD, and biochemical evidence of mixed dyslipidemia (having 2 of the following 3 lipid parameters: LDL-C >100 mg/dL, TG >200 mg/dL, and HDL-C <40 mg/dL)	N=300 12 weeks	Primary: Lipid and lipoprotein profiles Secondary: Not reported	Primary: Fenofibrate plus simvastatin significantly reduced dense VLDL-C compared to fenofibrate (P<0.001) and simvastatin (P<0.0001). Simvastatin significantly reduced IDL-C compared to fenofibrate (P<0.003). The percentage of LDL-C pattern B constituting total LDL-C was significantly reduced by fenofibrate (-13.7%; P<0.0001) and fenofibrate plus simvastatin (-11.1%, P<0.0001). There was no significant change with simvastatin (-2.4%; P=0.27).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs simvastatin 20 mg QD				Fenofibrate and fenofibrate plus simvastatin significantly increased the percentage of buoyant LDL-C constituting total LDL-C (-19.6%; P<0.0001 and -16.9%; P<0.0001, respectively). There was no significant change with simvastatin (-3.1%; P=0.06). Secondary: Not reported
Jones et al.[37] (2009) Fenofibric acid 135 mg QD vs low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs fenofibric acid 135 mg plus low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or	Pooled analysis of 3 AC, DB, MC, RCT Patients >18 years of age, with HDL-C <40 mg/dL (men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL ≥130 mg/dL	N=2,715 12 weeks	Primary: Mean percent change in HDL-C, TGs (fenofibric acid plus atorvastatin vs atorvastatin), and LDL-C (fenofibric acid plus atorvastatin vs fenofibric acid) Secondary: Mean percent change in non-HDL-C, VLDL-C, TC, apo B, and hsCRP; safety	Primary: Fenofibric acid plus low-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (18.1 vs 7.4%; P<0.001) and a greater mean percent decrease in TG (-43.9 vs -16.8%; P<0.001) compared to low-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-33.1 vs -5.1%; P<0.001) compared to fenofibric acid monotherapy. Fenofibric acid plus moderate-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (17.5 vs 8.7%; P<0.001) and a greater mean percent decrease in TG (-42.0 vs -23.7%; P<0.001) compared to moderate-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-34.6 vs -5.1%; P<0.001) compared to fenofibric acid monotherapy. No formal comparisons were made between the high-dose statin monotherapy group and the other treatment groups. Secondary: Greater improvements in non-HDL-C, VLDL-C, TC, and apo B were observed for fenofibric acid plus low-dose statin combination therapy compared to corresponding monotherapies (P≤0.001). Combination therapy was generally well tolerated, and safety profiles were similar to monotherapies. No rhabdomyolysis was reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atorvastatin 40 mg) QD vs fenofibric acid 135 mg QD plus moderate-dose statin QD vs high-dose statin (rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg) QD				
Bays et al.[38] (2008) Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) Extension study patients received the same type of statin that was used in the statin-containing arms of the controlled study in which	MC, OL Patients with mixed dyslipidemia completing 1 of 3 MC, PRO, DB, RCT 12-week studies were eligible	N=2,201 1 year	Primary: Safety, percent changes from baseline in TG, HDL-C, and LDL-C Secondary: Percent changes in non-HDL-C, VLDL-C, TC, apoB, and hs-CRP	Primary: Of the 2,201 patients who received at least one dose of fenofibric acid plus statin combination therapy, six patients (0.3%) died during the conduct of the ES; no death was considered by the investigator to be treatment related. Overall, 148 (6.7%) patients had treatment-emergent serious adverse events (fenofibric acid plus rosuvastatin, 7.2%; fenofibric acid plus simvastatin, 7.8%; fenofibric acid + atorvastatin 4.6%). The most common treatment-emergent serious adverse events were osteoarthritis, deep vein thrombosis, CAD, MI, and chest pain, diverticulitis, syncope, and intervertebral disc protrusion. A total of 1,856 patients (84.3%) had one or more treatment-emergent adverse events (fenofibric acid plus rosuvastatin, 83.1%; fenofibric acid plus simvastatin, 86.2%; fenofibric acid plus atorvastatin, 85.2%). The most frequently reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, and back pain. Among patients who received fenofibric acid monotherapy in a controlled

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
they participated				study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-22.0%), mean percent decrease in LDL-C (-38.1%), and mean percent increase in HDL-C (6.2%). Among patients who received moderate-dose statin monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-30.5%) and mean percent increases in HDL-C (13.1%) and LDL-C (3.1%). Among patients who received fenofibric acid plus low-dose statin combination therapy in a controlled study, there was an additional median percent decrease in TG (-4.2%), mean percent increase in HDL-C (4.8%), and mean percent decrease in LDL-C (-9.7%) after the statin dose was increased for 52 weeks. The group of patients who were treated with fenofibric acid plus moderate-dose statin in a controlled study and continued the same therapy in the extension study exhibited sustained improvements in lipid parameters throughout the course of therapy. For this group of patients, treatment with fenofibric acid plus moderate-dose statin combination therapy for a total of 64 weeks decreased TG from a mean baseline of 297.8 mg/dL to a mean final level of 138.0 mg/dL, decreased LDL-C from a mean baseline of 153.1 mg/dL to a mean final level of 94.2 mg/dL, and increased HDL-C from a mean baseline of 38.2 mg/dL to a mean final level of 47.7 mg/dL. Secondary: Among patients who received fenofibric acid monotherapy or moderate-dose statin monotherapy in the controlled studies, treatment with fenofibric acid plus moderate-dose statin combination therapy in the extension study resulted in additional mean percent decreases in non-HDL-C, VLDL-C, TC, and apo B, and median percent decrease in hsCRP that were sustained throughout 52 weeks of combination therapy. For patients initially treated with fenofibric acid plus low-dose statin

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				combination therapy, increasing the statin dose resulted in additional mean percent decreases in non-HDL-C, TC, and apo B and median percent decrease in hsCRP, which were sustained throughout the study.
Kipnes et al.[39] (2010) Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) ES patients received the same type of statin that was used in the statin-containing arms of the controlled study in which they participated.	ES, OL Patients with mixed dyslipidemia at the start of a 1 year, ES, OL	N=310 1 year (2 years of total therapy)	Primary: Safety and efficacy Secondary: Not reported	Primary: No deaths occurred during the two year trial. The incidence of serious adverse events was numerically highest with fenofibric acid plus rosuvastatin (14.9%) compared to fenofibric acid plus simvastatin (8.0%) or atorvastatin (5.8%). The incidences of adverse events were similar among all treatments as well (94.8, 90.0 and 97.7%). Adverse events tended to occur early in treatment, without the development of new types of adverse events over time. The most common treatment-related adverse events were muscle spasms (3.9%), increased blood creatine phosphokinase (3.5%), headache (2.9%), myalgia (2.9%), dyspepsia (2.3%) and nausea (2.3%). Rhabdomyolysis was not reported with any treatment. Nine patients discontinued therapy due to adverse events, with similar incidences among all treatments. Myalgia was the most common reason for discontinuation. No significant difference in the incidence of laboratory elevations was observed among the treatment groups. Incremental improvements in mean percentage changes in all efficacy variables were observed after the first visit in the year one ES (week 16). This effect was sustained for greater than two years and sizable mean percentage changes in all efficacy variables were observed at week 116. In the overall population, the mean percentage changes from baseline to week 116 in efficacy variables were: 17.4 (HDL-C), -46.4 (TG), -40.4 (LDL-C), -47.3 (non-HDL-C), -37.8 (TC) and -52.8% (VLDL-C). Significant differences among treatments were observed for non-HDL-C (-48.60±13.58 vs -41.70±13.10 vs -47.30±12.50%; *P*=0.011), TC (-38.70±12.16 vs -32.50±10.86 vs -38.60±10.85%; *P*=0.007) and VLDL-C (-56.80±25.17 vs -40.30±51.25 vs -51.20±35.42%; *P*=0.019). Secondary: Not reported
Farnier et al.[40] (2005) Fenofibrate 160	DB, MC, PC, RCT Men and women 18 to 75 years of age	N=619 12 weeks	Primary: Percent change in LDL-C from baseline to study	Primary: The mean percent change in LDL-C reduction was significantly greater in the micronized fenofibrate and ezetimibe group when compared to the other treatment groups (P<0.001 compared to micronized fenofibrate and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs ezetimibe 10 mg QD vs placebo	with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or 10-year CHD risk >20%		end point Secondary: Percent change in other lipid, non-lipid, and lipoprotein parameters from baseline to study end point	ezetimibe). These reductions were 13.4% in the ezetimibe group, 5.5% in the micronized fenofibrate group, and 20.4% in the micronized fenofibrate and ezetimibe group. Secondary: When compared to micronized fenofibrate or ezetimibe monotherapy, significant reductions in apo B, non-HDL-C and LDL-C were observed in the micronized fenofibrate and ezetimibe group; P<0.001. When compared to placebo, significant decreases in TG levels and significant increases in HDL-C level were observed in both the micronized fenofibrate plus ezetimibe and micronized fenofibrate treatment groups; P<0.001. The percent changes from baseline to study end point were as follows: -11.8% in TC, 3.9% in HDL-C, -11.1% in TG, and -6.1% in hsCRP in the ezetimibe group; -10.8% in TC, 18.8% in HDL-C, -43.2% in TG, and -28.0% in hsCRP in the micronized fenofibrate group; -22.4% in TC, 19.0% in HDL-C, -44.0% in TG, and -27.3% in hsCRP in the micronized fenofibrate and ezetimibe group (P<0.05 for all).
Tribble et al.[41] (2008) Ezetimibe 10 mg and fenofibrate 160 mg QD (FENO + EZE) vs ezetimibe 10 mg QD (EZE) vs fenofibrate 160 mg QD (FENO) vs	DB, MC, PC, RCT Patients 18 to 75 years of age with mixed hyperlipidemia (LDL-C 130 to 220 mg/dL and TG 200 to 500 mg/dL) and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=625 12 weeks	Primary: Changes in cholesterol mass within the major lipoprotein fractions and subfractions and LDL particle distribution profiles and particle size Secondary: Not reported	Primary: The effects of EZE, FENO, and FENO + EZE on VLDL subfractions were similar to those for VLDL overall. All active treatments reduced IDL-C. Treatment with FENO significantly reduced LDL-C1, LDL-C3, and LDL-C4 and significantly increased LDL-C2 compared to placebo. FENO + EZE produced a pattern of changes similar to those of FENO alone. The reductions in LDL-C1 and LDL-C3 were greater with the combination due to the added effects of EZE. There were no significant changes in cholesterol associated with Lp(a). Fenofibrate and FENO + EZE increased median HDL-C2 and HDL-C3 compared to EZE and placebo. In patients treated with EZE, there were reductions in VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL density distributions or changes in the HDL-C range.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				In patients treated with FENO, there were reductions in VLDL-C and IDL-C. HDL-C was increased and there was a shift in the distribution of LDL toward larger, more buoyant LDL particles with a small effect on LDL-C values overall. In patients treated with FENO + EZE, there were reductions in VLDL-C, IDL-C, and LDL-C. HDL-C was increased and there was a shift from smaller, more dense to larger, more buoyant LDL subfractions. EZE did not significantly affect LDL peak particle size. FENO and FENO + EZE increased LDL peak particle size. Secondary: Not reported
McKenney et al.[42] (2006) Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs ezetimibe 10 mg QD for 12 weeks, then fenofibrate 160 mg and ezetimibe 10 mg QD for 48 weeks	DB Patient who completed base study with mixed hyperlipidemia	N=576 48 weeks	Primary: Percent change in LDL-C from baseline of the base study to study end point in the extension Secondary: Percent change from baseline to study end point in TC, HDL-C, TG, non-HDL-C, apo B, apo AI, and hsCRP	Primary: Fenofibrate plus ezetimibe showed significantly greater percent reductions in LDL-C compared to fenofibrate alone (-22.0 vs -8.6; P<0.001). Secondary: Fenofibrate plus ezetimibe showed significantly greater percent reductions from baseline to extension study end point in TC (-23.2 vs -13.6; P<0.001), TG (-46.0 vs -41.0; P=0.002), non-HDL-C (-31.6 vs -19.4; P<0.001), and apo B (-25.2 vs -16.2; P<0.001) compared to fenofibrate. There was a significantly greater percent increase in HDL-C (20.9 vs 17.8; P=0.02) with fenofibrate plus ezetimibe vs fenofibrate alone. There was not a significantly greater percent increase in apo AI (10.1 vs 7.8; P=0.12) with fenofibrate plus ezetimibe vs fenofibrate alone. Reductions in median hsCRP levels were not different between treatments (-25.3 vs -21.1; P=0.46) for fenofibrate plus ezetimibe vs fenofibrate alone, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 12 weeks, then fenofibrate 160 mg for 48 weeks				
Ansquer et al.[43] (2009) Fenofibrate (Tricor®) 145 mg and ezetimibe 10 mg QD vs fenofibrate (Tricor®) 145 mg QD vs ezetimibe 10 mg QD	DB, MC, RCT Patients 18 to 70 years of age with type IIb dyslipidemia (LDL-C ≥160 mg/dL, TG 150 to 405 mg/dL) and ≥2 features of the metabolic syndrome according to the NCEP ATP III definition	N=60 12 weeks	Primary: Percentage change from baseline in TG and HDL-C Secondary: Percentage change in LDL-C, non-HDL-C, remnant-like particle cholesterol (RLP-C) and related parameters, change in glucose metabolism parameters, hsCRP, safety	Primary: Fenofibrate plus ezetimibe and fenofibrate reduced TG by -38.3% (P value not significant) and increased HDL-C to a similar extent (11.5 and 7.9%, respectively; P=0.282). Secondary: Fenofibrate plus ezetimibe reduced LDL-C by -36.2% compared to -22.4% with fenofibrate and -22.8% with ezetimibe (P<0.001 for both). Fenofibrate plus ezetimibe lowered non-HDL-C by -36.2% compared to fenofibrate (-24.8%) and ezetimibe (-20.9%) (P value not reported). There was no significant difference between fenofibrate plus ezetimibe and fenofibrate with regards to RLP-C (-36.2 vs -30.7%; P value not significant). Ezetimibe was less effective than fenofibrate plus ezetimibe (-17.3%; P<0.001). The effect of fenofibrate plus ezetimibe on LDL particle size (+2.1%) was similar to that of fenofibrate (+1.9%). Fenofibrate plus ezetimibe was more effective than monotherapy with fenofibrate or ezetimibe in reducing apo B (-33.3%). Fenofibrate plus ezetimibe had the same effect as fenofibrate on apo AI (+7.9 vs +5.1%, respectively) and apo AII (+24.2 vs +21.2%, respectively; P value not reported). Fenofibrate plus ezetimibe and fenofibrate reduced hsCRP to a similar degree. There was a higher incidence of treatment-related adverse events with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				fenofibrate/ezetimibe, which was primarily due to abnormal laboratory changes, including moderate increases in CK, liver enzymes, and blood creatinine.
Farnier et al.[44] (2007) Fenofibrate 160 mg QD and simvastatin-ezetimibe 20-10 mg QD vs fenofibrate 160 mg QD vs simvastatin-ezetimibe 20-10 mg QD vs placebo	DB, MC, PA, PC, RCT Patients 18 to 79 years old with mixed hyperlipidemia and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in TC, TG, HDL-C, non-HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C/HDL-C, apo B	Primary: Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction in LDL-C from baseline compared to the fenofibrate monotherapy group (45.8 vs 15.7%; P<0.05). There was no significant difference between LDL-C reduction seen with the simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (45.8 vs 47.1%; P>0.2). Secondary: Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction from baseline in non-HDL-C, TG, and apo B compared to the other treatment groups (P<0.01). There was no significant difference between TC reduction seen with the simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (38.7 vs 35.4%; P>0.05). Simvastatin-ezetimibe plus fenofibrate group exhibited significant increase from baseline in HDL-C compared to the simvastatin-ezetimibe group (18.7 vs 9.3%; P<0.01). Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction from baseline in LDL-C:HDL-C, TC:HDL-C compared to the simvastatin-ezetimibe group (P=0.03). There was no significant difference between the percentage of patients able to reach their LDL-C goal with the simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (88.5 vs 92.9%).
Farnier et al.[45] (2008) Fenofibrate 160 mg and ezetimibe-	RCT, DB, MC, PC Patients 18 to 79 years of age with mixed hyperlipidemia	N=611 12 weeks	Primary: Percent change in cholesterol associated with lipoprotein	Primary: The effects of ezetimibe-simvastatin, fenofibrate, and ezetimibe/simvastatin plus fenofibrate on VLDL subclasses were similar to those for VLDL-C overall.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 10-20 mg QD vs fenofibrate 160 mg QD vs ezetimibe-simvastatin 10-20 mg QD vs placebo	and no CHD, CHD-equivalent disease (except for type 2 diabetes), or CHD risk score >20% (as defined by NCEP ATP III), LDL-C 130 to 220 mg/dL and TG 150 to 500 mg/dL		subfractions (VLDL-C 1+2 and VLDL-C 3, IDL-C, LDL-C 1 to 4, Lp[a], HDL-C_2 and HDL-C_3, and changes in LDL particle size) Secondary: Not reported	The maximal changes in IDL-C are achieved by ezetimibe-simvastatin with little additional effect of fenofibrate. Significant reductions were observed for all LDL-C subfractions with ezetimibe-simvastatin treatment. When coadministered with fenofibrate, the effects of both treatments were evident. Ezetimibe-simvastatin plus fenofibrate resulted in a pattern of changes that were similar to fenofibrate monotherapy indicating that the change in LDL-C pattern was primarily a function of fenofibrate. There was no significant difference in cholesterol associated with Lp(a) among the treatment groups. Fenofibrate and ezetimibe-simvastatin plus fenofibrate led to similar increases in median HDL-C_2 and HDL-C_3 compared to ezetimibe-simvastatin and placebo. Ezetimibe-simvastatin did not significantly affect LDL particle size. Fenofibrate and ezetimibe-simvastatin plus fenofibrate increased LDL particle size. At the end of the study, the percentages of patients exhibiting LDL size pattern B was 64, 49, 14, and 17% in the placebo, ezetimibe-simvastatin, fenofibrate, and ezetimibe-simvastatin plus fenofibrate groups, respectively. Secondary: Not reported
Kumar et al.[46] (2009) Ezetimibe 10 mg/day plus fenofibrate 160 mg/day vs atorvastatin 10	RCT, XO Patients with hypercholesterolemia requiring pharmacotherapy	N=43 12 weeks	Primary: Percentage reduction of LDL-C Secondary: Percent changes from baseline in TC, HDL-C and TG	Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (P=0.46). Secondary: Both treatments provided similar improvements in TC (-25.1 vs -24.6%; P=0.806) and HDL-C (10.1 vs 8.9%; P=0.778). Combination therapy showed a trend towards a greater reduction in TGs (25.4 vs 14.5%; P=0.079), although there were no significant difference between the two treatments in terms of the improvement in TC:HDL-C (-29.0 vs -28.7%; P=0.904).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day				
Winkler et al.[47] (2009) Fluvastatin 80 mg/day plus fenofibrate 200 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 mg/day	MC, OL, RCT, XO Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist circumference ≥94 (men) or ≥80 cm (females) plus 1 of the following: TG ≥150 mg/dL, BP (≥85/≥130 mm Hg), FPG ≥100 mg/dL or prevalent type 2 diabetes	N=75 6 weeks	Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions Secondary: Not reported	Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only reached significance in patients without small, dense LDL (P=0.043, P=0.006 and P=0.20). Reductions in TG were only significant with fluvastatin plus fenofibrate compared to ezetimibe plus simvastatin in patients with small, dense LDL (P=0.029). Increases in HDL-C and apo AI were only significant with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate in patients without small, dense LDL (P=0.020 and P=0.015). In patients with small, dense LDL, apo AII was markedly increased by fluvastatin plus fenofibrate, whereas ezetimibe plus simvastatin had no or little effect. Although only significant in small, dense LDL patients, apo CIII was more effectively reduce by fluvastatin plus fenofibrate, while the reduction of apo CII was more pronounced with ezetimibe plus simvastatin in all patients. Secondary: Not reported
Wi et al.[48] (2010) Niacin ER 500 mg/day for 5 weeks, followed by 1,000 mg/day for 4 weeks, followed by 1,500 mg/day vs fenofibrate 160 mg/day After discontinuation of	OL, RCT Patients 20 to 79 years of age with TG 150 to 499 mg/dL and HDL-C <45 mg/dL	N=201 24 weeks (includes 8 week dietary run in period)	Primary: Percent change from randomization to week 16 in apo B/apo AI Secondary: Percent changes in other lipid parameters, levels of glucose metabolism-related parameters, hsCRP	Primary: Apo B/apo AI was reduced with both treatments with no difference between the two (P=0.47). The percent reduction in apo B was greater with niacin, whereas the percent elevation in apo AI was higher with fenofibrate. Secondary: TC significantly decreased with both treatments, and TG decreased and HDL-C increased. LDL-C increased with fenofibrate but decreased with niacin. The percent reduction in TC was greater with niacin (P=0.01). TG decreased significantly more with fenofibrate (P=0.045), whereas the percent elevation in HDL-C was not different between the two treatments (P=0.22). The percent change in LDL-C was significantly different with the two treatments (P<0.001). Lp(a) levels were reduced with niacin only, and the change was significantly different compared to fenofibrate (P<0.001). FPG levels decreased with fenofibrate and increased significantly with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
any lipid modifying drug, patients entered an 8 week dietary run in period.				niacin. HbA_{1c} levels increased with both treatments; the increase was borderline with fenofibrate and significant with niacin. The percent changes in FPG (P<0.001) and HbA_{1c} (P<0.001) levels were significantly different between the two treatments. Fasting insulin levels showed a borderline reduction with fenofibrate and a significant increase with niacin. HOMA-IR was decreased with fenofibrate and was increased with niacin. Percent changes of insulin (P<0.001) and HOMA-IR (P<0.001) were significantly different between the two treatments. hsCRP levels were significantly lowered with both treatments, but the percent change was greater with niacin (P=0.03).
Alrasadi et al.[49] (2008) <u>Protocol 1</u> Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID for 8 weeks <u>Protocol 2</u> Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	N=19 32 weeks	Primary: Percent changes in HDL-C and TC/HDL-C ratio Secondary: Not reported	Primary: <u>Protocol 1</u> The mean percent change in HDL-C was +6, -6, and +22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +19, -26, and -22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). <u>Protocol 2</u> The mean percent change in HDL-C was -2 and +18% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +32 and -32% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC/HDL-C (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs niacin SR 1 g BID and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study in Protocol 2.				
Balasubramanyam et al.[50] (2011) Usual care vs low saturated fat diet and exercise (D/E) vs D/E and fenofibrate 145 mg/day (Tricor®) vs D/E and niacin SR 2,000 mg/day	DB, PC, RCT Patients 21 to 65 years of age with hypertriglyceridemia (fasting TG >150 mg/dL) and receiving stable ART therapy for 6 months	N=191 24 weeks	Primary: Baseline changes in lipid parameters Secondary: Baseline changes in insulin sensitivity, glycemia, adiponectin, CRP, energy expenditure, and body composition	Primary: Patients receiving fenofibrate achieved significant improvements in TG (P=0.002), TC (P=0.02), and non-HDL-C (P=0.003), compared to patients receiving niacin who achieved significant improvements in HDL-C (P=0.03), and both groups of patients achieved significant improvements in TC:HDL-C (P=0.005 and P=0.01). The combination of D/E plus fenofibrate plus niacin provided maximal benefit, reducing TG (-52% vs usual care; P=0.003), increasing HDL-C (12% vs usual care; P<0.001), and decreasing non-HDL-C (-18.5% vs usual care; P=0.003) and TC:HDL-C (-24.5% vs usual care; P<0.001). Secondary: Of the secondary endpoints evaluated, there was an effect of niacin on FPG (P=0.0002), oral glucose tolerance test area under the curve for glucose (P=0.02), fasting insulin (P=0.03), HOMA-IR (P=0.008), insulin sensitivity index (P=0.007), and adiponectin (P<0.0001), and an effect of fenofibrate on creatinine (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Niaspan®) vs D/E and fenofibrate 145 mg/day and niacin SR 2,000 mg/day				
Roth et al.[51] (2009) <u>Phase I</u> Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks vs fenofibrate 130 mg (FENO) QD and placebo for 8 weeks <u>Phase II</u> Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks	DB, MC, PC, RCT Patients 18 to 79 years of age with Fredrickson type IV dyslipidemia, BMI 25 to 43 kg/m^2, and TG 500 to 1,300 mg/dL	N=167 16 weeks	Primary: Median percent change in TG Secondary: Additional lipid and cardiovascular risk factors	Primary: After eight weeks of therapy, median TG values were reduced from 649.5 to 267.5 mg/dL (-60.8%) with P-OM3 + FENO and from 669.3 to 310 mg/dL (-53.8%) with FENO monotherapy (P=0.059). There was no significant difference between the treatment groups (P=0.059). Secondary: LDL-C was significantly increased with P-OM3 + FENO compared to FENO monotherapy (48.2 vs 39.0%, respectively; P=0.030). There was no significant difference in non-HDL-C among the treatment groups (-8.2% for P-OM3 + FENO vs -7.1% for FENO; P=0.767). There was a greater reduction in VLDL-C with P-OM3 + FENO than with FENO monotherapy (-57.6 vs -47.6%, respectively; P=0.016). There was a greater reduction in RLP-C with P-OM3 + FENO than with FENO monotherapy (-72.0 vs -62.1%; P=0.029). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly reduced TGs compared to the end of the DB treatment period (-17.5%, P=0.003). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly increased LDL-C (+8.1%; P=0.001) compared to the group previously receiving P-OM3 + FENO (+0.4%). There was no significant change in non-HDL-C following the addition of P-OM3 to FENO. VLDL-C and RLP-C were significantly reduced by the addition of P-OM3 (-15.4%, P=0.030 and -25.8%, P=0.035, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in final lipid results for those who received P-OM3 + FENO for 16 weeks and those in which P-OM3 was added to FENO monotherapy during the OL phase of the study. In the pooled analysis of all patients enrolled in the eight week OL extension phase, the overall reductions of TGs and VLDL-C were -60.0 and -56.5%, respectively (P<0.001 for both). Non-HDLC and TC were also significantly reduced (P<0.001) over the 16 week treatment period in the pooled analysis. LDL-C increased 52.2% (P<0.001). There was no significant change in apo B at the end of the 16 week treatment study (P=0.544). The treatments were generally well tolerated and there was no significant difference in the safety profiles. The most adverse events were upper respiratory infection, nausea, diarrhea, constipation, gastroenteritis, dyspepsia, and headache.
Koh et al.[52] (2012) Fenofibrate 160 mg/day vs omega-3 fatty acids 2 g/day vs placebo	PC, PG, RCT, SB Patients with primary hypertriglyceridemia (>150 mg/dL)	N=50 2 months	Primary: Change in baseline lipid profile; change in baseline vasomotor function, hsCRP, and fibrinogen; change in baseline adiponectin, HbA_{1c}, and insulin resistance Secondary: Not reported	Primary: Placebo treatment significant reduced TG and TG:HDL-C, but increased LDL-C from baseline. Omega-3 fatty acids significantly reduced TG and TG:HDL-C from baseline. Fenofibrate significantly reduced T C, TG, apo B, TG:HDL-C, and non-HDL-C, and increased HDL-C and apo AI from baseline. Effects of fenofibrate on TC and T G were both significant compared to placebo (P<0.05). The magnitude of change in HDL-C, apo AI, TG:HDL-C, and non-HDL-C were significantly different when omega-3 fatty acids and fenofibrate therapy were compared, but both treatments resulted in comparable improvements in TG (P<0.05). Placebo did not significantly improve flow-mediated dilator response to hyperemia, but omega-3 fatty acids and fenofibrate significantly improved flow-mediated dilator response to hyperemia after two months when compared to baseline (P<0.001), and when compared to placebo (P<0.001). Brachial artery dilator responses to nitroglycerin were not significantly different between any of the therapies. Placebo and omega-3 fatty acids did not significantly change hsCRP and fibrinogen levels relative to baseline measurements. Fenofibrate significantly reduced hsCRP and fibrinogen levels after two months compared to baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.001) or when compared to placebo (P<0.05). Omega-3 fatty acids did not significantly change insulin, plasma adiponectin levels, or insulin sensitivity compared to placebo. Compared omega-3 fatty acids, fenofibrate significantly decreased fasting insulin (P=0.023) and increased plasma adiponectin (P=0.002) and insulin sensitivity (P=0.015). Secondary: Not reported
Koh et al.[53] (2006) Fenofibrate 200 mg QD and candesartan 16 mg QD vs fenofibrate 200 mg QD vs candesartan 16 mg QD	DB, PC, RCT, XO Patients with hypertriglyceridemia (≥150 mg/dL) and hypertension (≥140/90 mm Hg)	N=46 6 months	Primary: BP, lipid profile, inflammatory markers, vasomotor function, plasma malondialdehyde, adiponectin, and insulin resistance Secondary: Not reported	Primary: Fenofibrate, combined therapy, or candesartan therapy significantly reduced BP. However, combined therapy significantly reduced BP more than fenofibrate or candesartan alone (P<0.001). When compared to candesartan, fenofibrate or combined therapy significantly improved the lipoprotein profile. Fenofibrate alone or combined therapy significantly lowered TC, TG, apo B, and non-HDL-C levels (P<0.001 for all) and increased HDL-C levels (P<0.001) when compared to baseline. These reductions were significantly greater than those observed with candesartan alone (P<0.001). However, there were no significant differences between fenofibrate alone and fenofibrate plus candesartan for these parameters (P value not significant). All three treatment arms significantly improved flow-mediated dilator response to hyperemia. Combined therapy significantly decreased plasma malondialdehyde (a biomarker for oxidative stress), hsCRP, and soluble CD40L levels relative to baseline measurements. Importantly, these parameters were changed to a greater extent with combined therapy when compared to monotherapy (P<0.001, P=0.002, P=0.050, and P=0.032, respectively). Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. However, the magnitudes of these increases were not significantly different among the three therapies (P=0.246 for adiponectin levels and P=0.153 for insulin sensitivity).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Insua et al.[54] (2002) Gemfibrozil 900 mg daily vs fenofibrate 200 mg QD	DB, DD, RCT, XO Patients between the ages of 45 and 70 years with primary hyperlipo-proteinemia, Fredrickson phenotypes IIa and IIb	N=21 6 weeks	Primary: Cholesterol-lowering effectiveness Secondary: Not reported	Primary: Both drugs significantly reduced TC, calculated LDL-C, TG, apo B, and fibrinogen (P<0.01 for all calculations, except P<0.05 for fibrinogen with gemfibrozil therapy) and increased HDL-C (P<0.01). Neither drug affected Lp(a), whereas uric acid was reduced only by fenofibrate (P<0.01). The percentage decrease in TC and LDL-C was greater with fenofibrate compared to gemfibrozil (-22 vs -15%; P<0.02; and -27 vs -16%; P<0.02, respectively). In contrast, reductions in levels of TG (-54 vs -46.5%), apo B, and fibrinogen, as well as the increase in HDL-C (9% for both drugs), showed no significant difference between treatments. Separate analysis of patients with type IIb hyperlipoproteinemia showed essentially the same plasma lipid changes as for the overall group, but with greater modifications in TG and HDL-C concentrations. Secondary: Not reported
Corbelli et al.[55] (2002) Gemfibrozil (mean daily dose 1,200 mg) vs fenofibrate (mean daily dose of 201 mg)	RETRO Patients who were switched from gemfibrozil to fenofibrate, due to inadequate lipid response or adverse effects	N=92 23 months	Primary: Mean TC, TG, HDL-C, and non-HDL-C Secondary: Not reported	Primary: Compared to gemfibrozil, patients showed statistically significant improvements in mean TC, TG, HDL-C, and non-HDL (P<0.005). Specifically, more patients achieved a TG goal <200 mg/dL with fenofibrate (64%) compared to gemfibrozil (39%; P<0.0005). The study demonstrated that patients switched from gemfibrozil to fenofibrate due to an inadequate lipid response experienced significant improvements in lipid parameters for up to 18 months. Secondary: Not reported
Guyton et al.[56] (2000)	DB, MC, PC, RCT	N=173	Primary: Effect on HDL-C	Primary: Niacin 1,500 and 2,000 mg/day significantly increased HDL-C by 21 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Niacin ER (Niaspan®) titrated up to 1,000 mg at bedtime for 4 weeks, followed by 1,500 mg at bedtime for 4 weeks, followed by 2,000 mg at bedtime for 8 weeks vs gemfibrozil 600 mg BID	Patients 21 to 75 years of age with HDL-C ≤40 mg/dL, LDL-C ≤160 mg/dL or <130 mg/dL with atherosclerotic disease and TG ≤400 mg/dL	8 weeks	Secondary: Change in other lipoproteins, adverse effects	26%, respectively, compared to 13% with gemfibrozil (P<0.02). Secondary: Compared to gemfibrozil, niacin 1,500 and 2,000 mg/day significantly increased apo AI (9 and 11 vs 4%), reduced TC:HDL-C ratio (-17 and -22 vs -12%), reduced Lp(a) (-7 and -20 vs no change) and had no adverse effect on LDL-C (2 and 0 vs 9%; P<0.001 to P<0.02.). TG decreased by 40% with gemfibrozil compared to 16 and 29% with niacin 1,000 (P<0.001) and 2,000 mg/day (P<0.06). Effects on plasma fibrinogen levels were significantly favorable for niacin compared to gemfibrozil (-1 to -6% vs 5 to 9%, respectively; P<0.02). Flushing was significantly more frequent with niacin compared to gemfibrozil at every point (78 vs 10%; P values not reported). Flu syndrome occurred more frequently with niacin (P=0.006). Dyspepsia was more frequent with gemfibrozil (P=0.009).
Stalenhoef et al.[57] (2000) Omega-3-acid ethyl esters (Omacor*) 4 g/day vs gemfibrozil 1,200 mg/day	DB, DD, RCT Patients with primary hyper-triglyceridemia	N=28 12 weeks	Primary: Change in lipid profile, LDL-C subfraction profile Secondary: Not reported	Primary: Both omega-3-acid ethyl esters and gemfibrozil resulted in similar and significant decreases in serum TG, VLDL-TG and VLDL-C concentrations and increases in HDL-C and LDL-C (P=0.05 to P<0.001 from baseline and P=0.29 to P=1.00 between groups). Both therapies resulted in a more buoyant LDL-C subfraction profile (P=0.05 for omega-3-acid ethyl esters, P<0.01 for gemfibrozil and P=0.09 between groups in favor of gemfibrozil). Secondary: Not reported
van Dam et al.[58] (2001) Omega-3 acid ethyl esters (Omacor*) 4 g/day	RCT, DB Patients with hypertriglyceridemia (TG >400 mg/dL)	N=89 12 weeks	Primary: Percent change in TG Secondary: Percent change in TC, HDL-C,	Primary: The mean percent change in TG was -28.9% with omega-3 acid ethyl esters and -51.2% with gemfibrozil (P=0.007). Secondary: The mean percent change in HDL-C and TC were +1.2 and -10.2%, respectively, with omega-3 acid ethyl esters and +27.9 and -13.0%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs gemfibrozil 1,200 mg/day			VLDL-C	respectively, with gemfibrozil (P=0.012 and P=0.513, respectively). The mean percent change in VLDL-C was -11.8% with omega-3 acid ethyl esters and -19.4% with gemfibrozil (P=0.494).
Prevention of Coronary Heart Disease Events				
Keech et al.[59] (2005) FIELD Fenofibrate 200 mg QD vs placebo	DB, PC, RCT Patients aged 50 to 75 years with type 2 diabetes mellitus	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI) Secondary: Total cardiovascular events which included the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularization; total mortality	Primary: Coronary events occurred in 5.9% of patients on placebo and 5.2% of patients on fenofibrate (HR, 0.89; 95% CI, 0.75 to 1.05; P=0.16). There was a 24% reduction in nonfatal MI with fenofibrate (HR, 0.76; 95% CI, 0.62 to 0.94; P=0.010). There was a nonsignificant increase in coronary heart disease mortality (HR, 1.19; 95% CI, 0.90 to 1.57; P=0.22). Secondary: Total cardiovascular disease events were significantly reduced from 13.9 to 12.5% with fenofibrate (HR, 0.89; 95% CI, 0.80 to 0.99; P=0.035). There was a 21% reduction in coronary revascularization with fenofibrate (HR, 0.79; 95% CI, 0.68 to 0.93; P=0.003). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (P=0.18).
Tonkin et al.[60] (2012) FIELD Fenofibrate 200 mg QD vs placebo	Subgroup analysis of FIELD comparing the effect of fenofibrate on cardiovascular disease between patients with prior cardiovascular disease and those without Patients aged 50 to 75 years with type 2	N=9,975 (n=2,131 with prior cardio-vascular disease and n=7,664 without prior cardio-vascular disease) 5 years	Primary: Lipids and the effect of fenofibrate treatment, compliance with trial medication and use of other drugs, unadjusted effect of treatment on outcomes, components of total	Primary: There were small but significant differences between patients with and without prior cardiovascular disease in their pattern of lipid response to treatment. At 12 months after randomization, the effect of fenofibrate on increasing HDL-C and decreasing LDL-C and TG was greater in patients with no prior cardiovascular disease compared to those with prior cardiovascular disease (P<0.05 for all). At 24 months after randomization, difference in treatment effect between prior cardiovascular subgroups were observed for HDL-C (P=0.046) and TG (P=0.002). At trial end, differences were observed for LDL-C (P=0.01) and TG (P=0.006). Over the course of the trial, patients receiving placebo had a higher uptake of lipid-lowering therapy (mainly statins) compared to those receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	diabetes mellitus		cardiovascular disease, adjusted analyses of treatment effect Secondary: Not reported	fenofibrate (17 vs 8%). There was a higher uptake of statins among patients with prior cardiovascular disease compared those without and a slightly higher uptake of other cardiovascular medications. Patients with prior cardiovascular disease discontinued fenofibrate more often than those without prior cardiovascular disease (14 vs 9%). The unadjusted effect of fenofibrate on future total cardiovascular disease events differed by prior cardiovascular disease status (interaction P=0.05). There was an independently significant reduction in the risk of a cardiovascular disease event (HR, 0.81; 95% CI, 0.70 to 0.94; P=0.004) in the group without prior cardiovascular disease, whereas in the prior cardiovascular disease group, there was no significant effect of treatment (HR, 1.02; 95% CI, 0.86 to 1.20; P=0.9). There was a significant difference in treatment effect between those with and those without prior cardiovascular disease for coronary events (interaction P=0.03) but not stroke (P=0.56) or revascularization (P=0.053). For coronary events, there was an independently significant reduction in the risk of an event (HR, 0.75; 95% CI, 0.59 to 0.94; P=0.01) in the group without prior cardiovascular disease, whereas in the prior cardiovascular disease group, there was no significant effect of treatment (HR, 1.08; 95% CI, 0.84 to 1.38; P=0.55). After the adjustment for uneven uptake of statins and other cardiovascular disease medications across treatment arms, the treatment-by-prior-cardiovascular disease interaction term remained significant (statins only; P=0.05 and statins plus other cardiovascular disease medications; P=0.04). However, after adjustment for baseline covariates, differences in treatment effects were no longer significant (P=0.06). Secondary: Not reported
Ting et al.[61] (abstract) (2012) FIELD	Subgroup analysis of FIELD evaluating the effects of fenofibrate on cardiovascular and ESRD events,	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI), safety	Primary: The benefit of fenofibrate observed within the FIELD trial (HR, 0.89; 95% CI, 0.80 to 0.99; P=0.035), was not statistically different across eGFR groupings analyzed within this subgroup analysis (interaction P=0.2) (eGFR 30 to 50 mL/min/1.73m^2: HR, 0.68; 95% CI, 0.47 to 0.97;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fenofibrate 200 mg QD vs placebo	according to eGFR Patients aged 50 to 75 years with type 2 diabetes mellitus		Secondary: Not reported	P=0.035; eGFR ≥90 mL/min/1.73m^2: HR, 0.85; 95% CI, 0.70 to 1.02; P=0.08). ESRD rates were similar between treatment arms, without adverse safety signals of fenofibrate use in renal impairment. Secondary: Not reported
DAIS[62] (2001) Fenofibrate, micronized 200 mg QD vs placebo	PC, RCT Men and women with type 2 diabetes with good glycemic control, who had mild lipoprotein abnormalities typical of type 2 diabetes and at least one visible coronary lesion	N=418 3 years	Primary: Mean percentage stenosis, minimum coronary artery lumen diameter, mean segment diameter Secondary: Not reported	Primary: Plasma TC, HDL-C, LDL-C, and TG concentrations all changed significantly more from baseline in the fenofibrate group (N=207) compared to the placebo group (N=211). The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group (mean 2.11 vs 3.65; P=0.02), a significantly smaller decrease in minimum lumen diameter (-0.06 vs -0.10 mm; P=0.029), and an insignificant smaller decrease in mean segment diameter (-0.06 vs -0.08 mm; P=0.171). The trial was not powered to examine clinical end points. Secondary: Not reported
No authors listed.[63] ACCORD (2010) Fenofibrate 160 mg/day vs placebo All patients were receiving simvastatin.	DB, MC, PC, RCT Patients 40 to 79 years of age with type 2 diabetes and HbA_{1c} ≥7.5%, LDL-C 60 to 180 mg/dL, HDL-C <55 mg/dL for women or <50 mg/dL for men and TG <750 mg/dL if they were not receiving lipid therapy or <400	N=5,518 5 years	Primary: First occurrence of a major cardiovascular event (nonfatal MI, nonfatal stroke or death from cardiovascular causes) Secondary: Combination of the primary outcome plus	Primary: The annual rate of the primary outcome was 2.2% with fenofibrate and 2.4% with placebo (HR, 0.92; 95% CI, 0.79 to 1.08; P=0.32). Secondary: The annual rate of the primary outcome plus revascularization or hospitalization for CHF was 5.35% with fenofibrate and 5.64% with placebo (HR, 0.94; 95% CI, 0.85 to 1.05; P=0.30). The annual rate of major coronary disease events was 2.58% with fenofibrate and 2.79% with placebo (HR, 0.92; 95% CI, 0.79 to 1.07; P=0.26). The annual rate of nonfatal MI was 1.32% with fenofibrate and 1.44%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	mg/dL if they were		revascularization or hospitalization for CHF; a combination of a fatal coronary event, nonfatal MI or unstable angina; nonfatal MI; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; hospitalization or death due to heart failure	with placebo (HR, 0.91; 95% CI, 0.74 to 1.12; P=0.39). The annual rate of stroke was 0.38% with fenofibrate and 0.36% with placebo (HR, 1.05; 95% CI, 0.71 to 1.56; P=0.80). The annual rate of death from any cause was 1.47% with fenofibrate and 1.61% with placebo (HR, 0.91; 95% CI, 0.75 to 1.10; P=0.33). Rates for death from a cardiovascular cause were 0.72 and 0.83% (HR, 0.86; 95% CI, 0.66 to 1.12; P=0.26). The annual rate of fatal or nonfatal CHF was 0.90% with fenofibrate and 1.09% with placebo (HR, 0.82; 95% CI, 0.62 to 1.05; P=0.10).
Bonds et al.[64] (2012) ACCORD Fenofibrate 160 mg/day vs placebo All patients were receiving simvastatin.	Subgroup analysis of ACCORD, evaluating outcomes in patients with a fenofibrate-associated creatinine increase (increase in serum creatinine of ≥20% from baseline to month 4 in patients receiving fenofibrate) Patients 40 to 79 years of age with type 2 diabetes and HbA_{1c} ≥7.5%, LDL-C 60 to 180 mg/dL, HDL-C <55 mg/dL for women or <50 mg/dL for men and	N=1,212 (patients who experienced a fenofibrate-associated creatinine increase) 5 years	Primary: Characteristics predicting creatinine elevation Secondary: Long-term renal and cardiovascular outcomes	Primary: Patients who were older, male, used an angiotensin converting enzyme-inhibitor at baseline, used a thiazolidinedione at four months post-randomization, had baseline cardiovascular disease, and had lower baseline serum creatinine and LDL-C were all more likely to meet the criteria for fenofibrate-associated creatinine increase). Secondary: No differences in study outcomes were seen by fenofibrate-associated creatinine increase; there was no increase in renal disease or cardiovascular outcome observed in patients demonstrating fenofibrate-associated creatinine increases.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	TG <750 mg/dL if they were not receiving lipid therapy or <400 mg/dL if they were			
Davidson et al.[65] (2014) FIRST Fenofibric acid 135 mg vs placebo All patients on background atorvastatin	DB, MC, PC, RCT Patients with mixed dyslipidemia (fasting TG ≥150 mg/dL; HDL-C ≤45 [men] or 55 mg/dL [women]; LDL-C ≤100 mg/dL once and averaging ≤105 mg/dL) and a history of CHD or risk equivalent	N=682 104 weeks	Primary: Between-group difference in the rate of change from baseline through week 104 of the mean posterior-wall cIMT Secondary: Ranked multiple testing plan including measures of: maximal posterior- and anterior-wall cIMT of common carotid artery, internal carotid artery, and carotid bifurcation	Primary: The primary end point was −0.006 mm/y (FA plus atorvastatin group, −0.006 mm/y; atorvastatin monotherapy group, 0.000 mm/y), but did not reach statistical significance (P=0.22). Secondary: Secondary cIMT end points were not statistically different between treatment groups in the overall study population. The significance of between-treatment group differences varied among the lipid parameters. Starting at the first postbaseline assessment and continuing through week 104, fenofibric acid plus atorvastatin therapy resulted in significant improvements, compared with atorvastatin monotherapy, in HDL-C (week 104 mean change, +8.3 vs +3.6%), TG (−31.3 vs –2.3%, respectively), and non–HDL-C (−3.3 vs +4.9%). Fenofibric acid plus atorvastatin therapy resulted in LDL-C values that were significantly higher versus atorvastatin monotherapy through week 52, but no significant difference was observed subsequently through week 104.
Frick et al.[66] (1987) Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, RCT Asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive pretreatment measurements)	N=4,081 5 years	Primary: Risk of CHD measured by incidence of cardiac events Secondary: Total mortality	Primary: There were minimal changes in serum lipid levels in the placebo group. The cumulative rate of cardiac end points at five years was 27.3 per 1,000 in the gemfibrozil group and 41.4 per 1,000 in the placebo group, a reduction of 34% in the incidence of CAD (95% CI, 8.2 to 52.6; P<0.02; two-tailed test). The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. Secondary: There was no difference between the groups in the total death rate, nor did the treatment influence the cancer rates.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Frick et al.[67] (1993) Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, RCT Individuals who exhibited symptoms and signs of possible CHD during screening in the Helsinki Heart Study	N=311 5 years	Primary: Risk of CAD measured by incidence of cardiac events Secondary: Total mortality	Primary: The end point rate, consisting of fatal and nonfatal MI and cardiac death, did not differ significantly between the placebo and gemfibrozil groups. Since there were key prognostic factors missing (e.g., true prevalence of CHD, extent of coronary artery obstructions, degree of left ventricular dysfunction, and their distribution in the groups render the results less reliable), the data cannot be used to refute the thesis that treatment of dyslipidemia in manifest CHD is successful. Secondary: Total mortality did not differ significantly between the placebo and gemfibrozil groups.
Heinonen et al.[68] (1994) Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, MC Asymptomatic middle-aged men (40 to 55 years of age) with non-HDL-C greater than or equal to 200 mg/dL in 2 consecutive pretreatment measurements)	N=2,046 3.5 years	Primary: Definite fatal and nonfatal CHD events Secondary: Not reported	Primary: During the post-trial period the numbers of definite CHD events in both groups (54 vs 47; P value not significant) were smaller than expected without treatment, namely a reduction of around 40% for the original treatment groups. The mean incidence rates were in fact similar to that in the placebo group five years earlier. Cardiovascular mortality over the entire study period was similar but all-cause mortality was slightly higher among men of the original gemfibrozil group compared to the placebo group men (P=0.19). Secondary: Not reported
Huttunen et al.[69] (1994) Gemfibrozil 600 mg BID vs placebo	ES Asymptomatic adult patients with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive pretreatment measurements)	N=4,081 8.5 years (follow-up)	Primary: Gastrointestinal symptoms, surgery, strokes, cancer incidence, morality by cause Secondary: Not reported	Primary: A first occurrence of a moderate to severe gastrointestinal side effect, mainly dyspepsia and abdominal pain, was reported by 20.1 and 15.1% of patients receiving gemfibrozil and placebo during the original five year trial (P<0.001). Side effects were reported at a consistently lower rate during the post-trial follow up than during the DB trial period. After switching from placebo to gemfibrozil, 4.6% of patients interrupted treatment as a result of adverse events (3.7% due to gastrointestinal symptoms). There was a nonsignificant excess of some illnesses and surgical procedures with gemfibrozil during the five year trial period. During the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				3.5 year post trial follow-up, cholecystectomies and appendectomies continued to be more common with gemfibrozil. Strokes due to any cause were slightly less common with gemfibrozil. Ischemic strokes continued to occur less frequently in the original gemfibrozil groups, whereas hemorrhagic strokes were about equal post-trial. The cumulative incidences of malignancies and cancer cases by type during the 8.5 years of follow-up were similar, except basal cell skin carcinoma (16 vs 9; *P*=0.18). Over the 8.5 year follow up there were 101 deaths with gemfibrozil and 83 deaths with placebo. The distributions by causes of death did not differ significantly (*P*=0.12). The difference in cancer-specific deaths (30 vs 18) was mainly because of cancer deaths during the post-trial follow up (20 vs 7), while post-trial cardio- and cerebrovascular mortality was equal (25 vs 23, respectively). Deaths caused by cerebrovascular accidents were similar during the entire 8.5 year follow up (8 vs 6). There were fewer fatal cerebral infarctions (1 vs 5) and more fatal intracranial hemorrhages (7 vs 1) with gemfibrozil. The excess mortality due to accidents or violence was reversed during the post-trial follow up, resulting in approximately equal numbers by the end of the trial. Total mortality with the two treatments remained almost equal during the trial period and the first year of the post-trial follow up; the excess mortality emerged towards the end (*P*=0.19). Secondary: Not reported
Robins et al.[70] (2001) VA-HIT Gemfibrozil 1,200 mg daily vs	DB, MC, PC, RCT Men with a history of CHD who had low HDL-C levels and low LDL-C levels	N=2,531 7 years	Primary: Nonfatal MI or death from coronary causes Secondary: Not reported	Primary: Compared to placebo, gemfibrozil showed a 22% decreased risk of nonfatal MI or death due to CHD (17.3 vs 21.7%; P=0.006). Compared to placebo, gemfibrozil showed a 24% decreased risk for nonfatal MI, death due to CHD or confirmed stroke (20 vs 26%; P<0.001). A nonsignificant difference was seen in all-cause mortality with gemfibrozil compared to placebo (15.7 vs 17.4%; P=0.23).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Concentrations of HDL-C were inversely related to CHD events. Multivariable Cox proportional hazards analysis showed that CHD events were reduced by 11% with gemfibrozil for every 5 mg/dL (0.13 mmol/L) increase in HDL-C (P=0.02). Events were reduced even further with gemfibrozil beyond that explained by increases in HDL-C values, particularly in the second through fourth quintiles of HDL-C values during treatment. During gemfibrozil treatment, only the increase in HDL-C significantly predicted a lower risk of CHD events; according to multivariable analyses, neither TG nor LDL-C levels at baseline or during the trial predicted CHD events. Secondary: Not reported
Rubins et al.[71] (1999) Gemfibrozil 1,200 mg/day vs placebo	DB, MC, PC, RCT Men <74 years of age with CHD, HDL-C ≤40 mg/dL, LDL-C ≤140 mg/dL, TG ≤300 mg/dL and no serious coexisting conditions	N=2,531 5.1 years (mean follow up)	Primary: Combined incidence of nonfatal MI or death from CHD Secondary: Incidence of stroke, death from any cause, TIA, revascularization procedures, carotid endarterectomy and hospitalization for unstable angina or CHF	Primary: The combined primary endpoint occurred in 21.7 vs 17.3% of patients receiving placebo and gemfibrozil, which led to gemfibrozil being associated with a reduction of 22% (95% CI, 7 to 35; P=0.006). The effect was consistent for both components of the endpoint, but was only significant for a reduction in nonfatal MI (death from CHD, 22%; 95% CI, -2 to 41; P=0.07 and nonfatal MI, 23%; 95% CI, 4 to 38; P=0.02). The beneficial effect of gemfibrozil did not become apparent until about two years after randomization. Secondary: Gemfibrozil was not associated with a reduction in the incidence of stroke (6.0 vs 4.6%; RR reduction, 25%; 95% CI, -6 to 47; P=0.10). Gemfibrozil resulted in a RR reduction of 24% for the combined outcome of death from CHD, nonfatal MI or confirmed stroke (95% CI, 11 to 36; P<0.001). Gemfibrozil was associated with a significant reduction in the risk of TIA (RRR, 59%; 95% CI, 33 to 75; P<0.001). Gemfibrozil was associated with a significant reduction in the risk of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				carotid endarterectomy (RR reduction, 65%; 95% CI, 37 to 80; P<0.001). The rates of death from any case, coronary revascularization, hospitalization for unstable angina and cancer did not differ significantly between treatments.
Saha et al.[72] (2007) Fibrate therapy (bezafibrate*, clofibrate*, fenofibrate, gemfibrozil)	MA, SR (10 RCTs) Patients receiving fibrate therapy for the prevention of cardiovascular events (primary and secondary prevention)	N=36,489 Mean duration of follow up ≥1 year (32 months to 18 years)	Primary: All-cause mortality, cardiovascular and non-cardiovascular mortality, fatal and nonfatal MI and stroke Secondary: Incidence of cancer and cancer related mortality	Primary: On pooled MA, the use of fibrate therapy tended to increase all-cause mortality (pooled OR, 1.07; P=0.08) and significantly increased the odds of noncardiovascular mortality by about 16% (pooled OR, 1.16; P=0.004). Fibrate therapy had no significant effect on cardiovascular mortality, with a pooled OR of 0.98 (P=0.68). The use of fibrate therapy did not affect the occurrence of fatal MI (pooled OR, 0.96; P=0.76), but significantly reduced the odds of nonfatal MI by about 22% (pooled OR, 0.78; P<0.00001). Fibrate therapy also had no significant effect on stroke, with a pooled OR of 0.96 (P=0.56). Secondary: The use of fibrates was not associated with an increase in the odds of developing cancer (pooled OR, 1.00; P=0.98) or cancer related mortality (pooled odds ratio, 1.11; P=0.17). Subgroup analyses revealed that the risk of all-cause mortality did not significantly differ among the various fibrates used. Noncardiovascular mortality was significantly higher with the use of clofibrate on pooled analysis of data from two primary prevention trials (pooled OR, 1.35; 95% CI, 1.13 to 1.62; P=0.001). The odds of cardiovascular mortality tended to be lower with gemfibrozil with a pooled OR of 0.77 (P=0.05), whereas neither bezafibrate nor fenofibrate had any significant effect on mortality. The odds of nonfatal MI were lower with gemfibrozil (pooled OR, 0.72; P=0.001) than with bezafibrate (pooled OR, 0.78; P=0.02) or fenofibrate (pooled OR, 0.77; P=0.01). No significant differences were observed among the different fibrates with regard to their effects on fatal MI, stroke, cancer or cancer related mortality.
Jun et al.[73] (2010) Fibrate therapy	MA, SR (18 PRO, RCTs) Demographics not	N=45,058 Duration varied	Primary: Major cardiovascular events, coronary	Primary: Data for coronary events were available from 16 trials, including 44,667 patients in whom 4,552 coronary events were recorded.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(bezafibrate*, clofibrate*, etofibrate*, fenofibrate and gemfibrozil) vs placebo	reported		events, stroke, heart failure, coronary revascularization, all-cause mortality, cardiovascular death, nonvascular death, sudden death, new onset albuminuria, drug related adverse events Secondary: Not reported	Overall, fibrate therapy reduced the risk of coronary events by 13% (RR, 0.87; 95% CI, 0.81 to 0.93; P<0.0001). Ten trials, including 42,131 patients, reported 2,485 nonfatal coronary outcomes with fibrate therapy, reducing the risk by 19% (RR, 0.81; 95% CI, 0.75 to 0.89); P<0.0001). For the 1,740 coronary deaths recorded in 13 trials no effect was noted (RR, 0.93; 95% CI, 0.85 to 1.02; P=0.116). Effects on coronary revascularization were reported in four trials, including 15,834 patients whom 1,737 events were reported, with fibrate therapy significantly reducing the risk by 12% (RR, 0.88; 95% CI, 0.78 to 0.98; P=0.025). A cumulative MA of all trials reporting coronary outcomes demonstrated consistent benefit from fibrate therapy on the risk of coronary events. Eight trials, including 27,021 patients, reported 1,391 stroke events, with no evidence that fibrate therapy protected against stroke risk (RR, 1.03; 95% CI, 0.91 to 1.16; P=0.687). Three trials, including 8,581 patients, reported 584 heart failure events, with no evidence that fibrate therapy protected against heart failure risk (RR, 0.94; 95% CI, 0.65 to 1.37; P=0.759). Sixteen trials, including 44,813 patients, reported 3,880 deaths, with six trials reporting separate data for vascular death (22,066 patients with 1,545 reported vascular deaths) and five trials providing separate data for sudden death (12,277 patients reported 596 sudden deaths). No effect of fibrate therapy on the risk of all-cause mortality (RR, 1.00; 95% CI, 0.93 to 1.08; P=0.918), vascular mortality (RR, 0.97; 95% CI, 0.88 to 1.07; P=0.587) or sudden death (RR, 0.89; 95% CI, 0.74 to 1.06; P=0.190) was noted. An increased risk of nonvascular mortality was noted; however, this finding did not reach significance (RR, 1.10; 95% CI, 0.995 to 1.21; P=0.063). Three trials reported on the progression of albuminuria, including 15,731

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients and 3,859 events, with fibrate therapy reducing the risk by 14% (RR, 0.86; 95% CI, 0.75 to 0.98; P=0.028). Four trials reported data for total adverse events (17,413 patients reporting 225 events), demonstrating no significant increase in the risk of serious drug-related adverse events (RR, 22%; 95% CI, -9 to 61; P=0.19). Fibrate therapy did not significantly increase the risk of rhabdomyolysis (RR, 35%; 95% CI, -59 to 439; P=0.42), muscle abnormalities (RR, 0%; 95% CI, -1 to 2; P=0.69), gastrointestinal disorders (RR, 8%; 95% CI, -1 to 18; P=0.08) and gallbladder disease (RR, 19%; 95% CI, -11 to 60; P=0.24). Fibrate therapy was associated with an increase in creatinine (RR increase, 99%; 95% CI, 46 to 270; P<0.0001). Secondary: Not reported

*Agent not available within the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SR=sustained-release
Study abbreviations: AC=active comparator, DB=double-blind, DD=double dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, PA=parallel arm, PC=placebo controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective study, SB=single-blind, SR=systematic review, XO=crossover
Miscellaneous abbreviations: apo=apolipoprotein, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BP=blood pressure, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, cIMT=carotid intima-media thickness, CRP=C-reactive protein, eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HOMA-IR=Homeostasis Model of Assessment-Insulin Resistance, HR=hazard ratio, hsCRP=high sensitivity C-reactive protein, ICAM-1=intercellular adhesion molecule-1, IDL-C=intermediate-density lipoprotein-cholesterol , LDL-C=low-density lipoprotein cholesterol, Lp(a)=Lipoprotein(a), MI=myocardial infarction, MMP9=matrix metallopeptidase 9, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, RLP=remnant like particle cholesterol, RR=relative risk, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TRL=triglyceride rich lipoproteins, VCAM-1=vascular cell adhesion molecule-1, VLDL-C=very low-density lipoprotein cholesterol

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 Fibric Acid Derivatives

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Fenofibrate	capsule, tablet	Fenoglide®*, Lipofen®*	$$$$$	$$
Fenofibrate, micronized	capsule*	Antara®*	$$$$$	$$
Fenofibrate, nanocrystallized	tablet	Tricor®*	$$	$
Fenofibric acid	delayed-release capsule, tablet	Trilipix®*	$$$$$	$
Gemfibrozil	tablet	Lopid®*	$$$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The fibric acid derivatives are approved for the treatment of hypertriglyceridemia, primary hypercholesterolemia, and mixed dyslipidemia.[1-8] They decrease triglycerides by 20 to 50% and increase high-density lipoprotein cholesterol (HDL-C) by 10 to 35%. They can also lower low-density lipoprotein cholesterol (LDL-C) by 5 to 20%; however, LDL-C may increase in patients with hypertriglyceridemia.[9] All fibric acid derivatives are available in a generic formulation.

In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant, or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels and are recommended in patients with established coronary heart disease (CHD) or CHD equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy. The fibric acid derivatives are considered an option in patients who are unable to take a statin, but are typically reserved for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low HDL-C. They can also be considered an option for the treatment of patients with CHD who have low levels of LDL-C and atherogenic dyslipidemia. Guidelines do not give preference to one fibric acid derivative over another.[9,12-19] In 2016, the FDA removed the approved indication for coadministration of statins and fibrate products due to a lack of cardiovascular benefit.[74]

A warning/precaution for hepatotoxicity has been added to the labeling of the fibric acid derivatives. Serious drug-induced liver injury, including liver transplantation and death, have been reported postmarketing with these agents. Drug-induced liver injury has been characterized as hepatocellular, chronic active, and cholestatic hepatitis, and cirrhosis has occurred in association with chronic active hepatitis. These agents are contraindicated in patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities. Liver function, including serum ALT, AST, and total bilirubin should be monitored.[1-8]

The American College of Cardiology/American Heart Association released guidelines in 2013 which support initiating a statin in patients with established atherosclerotic cardiovascular disease (ASCVD). According to these recommendations, percent reduction in LDL-C is an indicator of response and adherence to therapy, but treating to a targeted level is not a primary goal.[16] Combination therapy can be considered on an individual basis, but studies of combination therapy have generally not shown benefit beyond statin monotherapy. Additionally, if patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.[16,17] The 2018 American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol recommend using an LDL-C threshold of 70 mg/dL to consider the addition of non-statins to statin therapy in very high-risk ASCVD patients.[17]

Clinical trials have demonstrated that the fibric acid derivatives can effectively lower triglycerides and increase HDL-C, as well as positively impact other lipid/lipoprotein parameters. Complementary lipid effects were also observed in clinical trials when fibric acid derivatives were coadministered with ezetimibe and statins.[25-58] In the FIELD trial, fenofibrate was associated with a nonsignificant reduction in CHD events in patients with type 2 diabetes, as well as a non-significant increase in total and CHD. However, fenofibric was associated with a significant reduction in total cardiovascular disease events and revascularization compared to placebo.[59] Furthermore, in the ACCORD trial, there was no difference between combination therapy with fenofibrate and simvastatin and monotherapy with simvastatin in the annual rate of first occurrence of major cardiovascular events in high-risk type 2 diabetics.[63] In the Helsinki Heart Study, gemfibrozil was associated with a significant reduction in CHD in asymptomatic men with dyslipidemia compared to placebo.[66] In a secondary prevention component of the Helsinki Heart Study, there was no difference observed between gemfibrozil and placebo in the incidence of fatal and nonfatal myocardial infarction and cardiac death.[67] Overall, because of chemical, pharmacological, and clinical similarities between the fibric acid derivatives, the findings from these studies may apply to all of the agents in this class.[1-9,11,12]

There is insufficient evidence to support that one brand fibric acid derivative 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 fibric acid derivatives 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 fibric acid derivative 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of HMG-CoA Reductase Inhibitors
AHFS Class 240608
February 7, 2024

I. Overview

The antilipemic agents are categorized into six different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, HMG-CoA reductase inhibitors (statins), and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The statins include single entity agents (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), as well as fixed-dose combination products (amlodipine-atorvastatin and ezetimibe-simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors. Statins also decrease the release of lipoproteins from the liver.[1-11] Depending on the agent selected, the statins can decrease LDL-C by 18 to 60% when used as monotherapy.[12-14] The effects on LDL-C are dose-dependent and log-linear. There is an additional 6% reduction in LDL-C with each doubling of the dose. The statins also decrease triglycerides by 7 to 30% and increase high-density lipoprotein cholesterol (HDL-C) by 5 to 15%.[14]

Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.[8] Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension, chronic stable angina, and vasospastic angina, as well as to reduce the risk of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease.[2] Previously, extended-release niacin was available in combination with statins as Advicor® (niacin extended-release-lovastatin) and Simcor® (niacin extended-release-simvastatin). Both drugs were voluntarily taken off of the market at the end of 2015. The FDA withdrew approvals it had previously given for use of niacin and fenofibric acid with statins to treat high cholesterol, citing a lack of cardiovascular benefit.[15]

The HMG-CoA reductase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The lipid-lowering effects of the statins are noted in Table 2. Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, amlodipine-atorvastatin, and ezetimibe-simvastatin are available in a generic formulation. This class was last reviewed in February 2022.

Table 1. HMG-CoA Reductase Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Atorvastatin	suspension, tablet	Atorvaliq®, Lipitor®*	atorvastatin
Fluvastatin	capsule, extended-release tablet	Lescol XL®*	fluvastatin
Lovastatin	extended-release tablet, tablet*	Altoprev®	lovastatin
Pitavastatin	tablet	Livalo®, Zypitamag®	none
Pravastatin	tablet	N/A	pravastatin
Rosuvastatin	sprinkle capsule, tablet	Ezallor®	rosuvastatin
Simvastatin	tablet	Zocor®*	simvastatin
Combination Products			
Amlodipine and atorvastatin	tablet	Caduet®*	amlodipine-atorvastatin

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ezetimibe and simvastatin	tablet	Vytorin®*	ezetimibe-simvastatin

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

Table 2. Lipid-lowering Effects of the HMG-CoA Reductase Inhibitors*[1-13]

Generic Name(s)	Total Cholesterol ↓ (%)	LDL-C ↓ (%)	Triglycerides ↓ (%)	HDL-C ↑ (%)
Single Entity Agents				
Atorvastatin	25 to 58	27 to 60	17 to 53	5 to 14
Fluvastatin	16 to 25	22 to 38	12 to 25	2 to 11
Lovastatin	16 to 34	21 to 42	10 to 27	5 to 12
Pitavastatin	22 to 35	31 to 45	13 to 22	1 to 8
Pravastatin	16 to 33	22 to 41	10 to 24	1 to 14
Rosuvastatin	24 to 46	28 to 63	10 to 43	3 to 22
Simvastatin	19 to 52	26 to 51	8 to 41	7 to 16
Combination Products				
Amlodipine and atorvastatin	25 to 58	27 to 60	17 to 53	5 to 14
Ezetimibe and simvastatin	31 to 43	45 to 60	23 to 31	6 to 10

*Includes studies in the prescribing information. Data are mean changes from baseline; data are pooled from different studies and may not be directly comparable.
HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the HMG-CoA reductase inhibitors are summarized in Table 3.

Table 3. Treatment Guidelines Using the HMG-CoA Reductase Inhibitors

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[16]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces

Clinical Guideline	Recommendation
	a marked reduction of LDL-C and a striking rise in HDL-C. Treatment of heterozygous familial hypercholesterolemia • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). Treatment of homozygous familial hypercholesterolemia • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). Treatment of familial defective apolipoprotein B-100 • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. Treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)[14]**	General recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant, or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients

Clinical Guideline	Recommendation
	with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout, and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <u>Fibric acid derivatives (fibrates)</u> • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <u>Omega-3 fatty acids</u> • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2017)[17] and Executive Summary (2020)[18]**	<u>Cholesterol Goals</u> • For patients at low risk for ASCVD (i.e., no risk factors), goals of LDL-C<130 mg/dL, non-HDL-C<160 mg/dL, and TG<150 mg/dL are recommended. • For patients at moderate risk for ASCVD (i.e., two or fewer risk factors and a calculated 10-year risk of <10%), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at high risk for ASCVD (i.e., two or more risk factors and a 10-year risk between 10% and 20% or who have diabetes or stage ≥3 CKD with no other risk factors), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at very high risk for ASCVD (i.e., established clinical ASCVD or recent hospitalization for ACS, carotid or peripheral vascular disease, or 10-year risk >20%; diabetes with one or more risk factor(s); CKD stage 3 or higher with albuminuria; or HeFH), goals of LDL-C<70 mg/dL, non-HDL-C<100 mg/dL, apo B<80 mg/dL, and TG<150 mg/dL are recommended. • For individuals at extreme risk (i.e., progressive ASCVD including unstable angina that persists after achieving an LDL-C <70 mg/dL; established clinical ASCVD in individuals with diabetes, CKD stage 3 or higher, and/or HeFH);

Clinical Guideline	Recommendation
	history of premature ASCVD (<55 years of age for males or <65 years of age for females), goals of LDL-C<55 mg/dL, non-HDL-C<80 mg/dL, apo B<70 mg/dL, and TG<150 mg/dL are recommended. • An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100 to 129 mg/dL considered "borderline" and 130 mg/dL or greater considered "high" (based on recommendations from the American Academy of Pediatrics). • Due to its potential cardioprotective role, HDL-C should be >40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C. <u>General Recommendations</u> • A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes and patient education with pharmacotherapy as needed to achieve evidence based targets. • A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include ≥30 minutes of moderate-intensity physical activity [consuming 4 to 7 kcal/min] four to six times weekly, with an expenditure of ≥200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities. • Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs. • In addition to aerobic activity, muscle-strengthening activity is recommended at least two days a week. • For adults, a reduced-calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains (primarily whole grains), fish, and lean meats is recommended. • For adults, the intake of saturated fats, trans-fats, and cholesterol should be limited, while LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10 to 25 g/day). • Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children. • Excessive alcohol intake should be avoided. • Tobacco cessation should be strongly encouraged and facilitated. • In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals. <u>Statins</u> • Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. • For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction. • In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered. • Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, who also have at least one additional risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70

Clinical Guideline	Recommendation
	mg/dL. • Extreme risk individuals should be treated with statins to target an even lower LDL-C treatment goal of <55 mg/dL. <u>Fibrates</u> • Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). • Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add fibrate. • In patients treated with a statin and icosapent ethyl with TG≥150 mg/dL, a fibrate may be considered. <u>Omega-3 Fish Oil</u> • Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose. • Omega-3 should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add omega-3. <u>Niacin</u> • Niacin therapy is recommended principally as an adjunct for reducing TG. • Niacin therapy should not be used in individuals aggressively treated with statin due to absence of additional benefits with well-controlled LDL-C. • Niacin should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add niacin. • In patients treated with a statin and icosapent ethyl with TG>150 mg/dL, niacin may be considered. <u>Icosapent Ethyl</u> • Icosapent ethyl (two grams twice daily) should be added to a statin in any patient with established ASCVD or diabetes with two or more ASCVD risk factors and triglycerides between 135 to 499 mg/dL to prevent ASCVD events. <u>Bile Acid Sequestrants</u> • Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG. <u>Cholesterol Absorption Inhibitors</u> • Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals. • Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk. <u>PCSK9 Inhibitors</u> • Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in

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	individuals with FH. • PCSK9 inhibitors should be considered in patients with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals. <u>Combination Therapy</u> • Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal. <u>Special Considerations: Women</u> • Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient. • Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended. <u>Special Considerations: Children and Adolescents</u> • Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, and particularly for those satisfying the following criteria: o LDL-C ≥190 mg/dL o LDL-C ≥160 mg/dL and the presence of two or more cardiovascular risk factors, even after vigorous intervention o Family history of premature ASCVD (before 55 years of age), or o Having overweight, obesity, or other elements of the insulin resistance syndrome <u>Follow-up and Monitoring</u> • Reassess individuals' lipid status six weeks after therapy initiation and again at six-week intervals until the treatment goal is achieved. • While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals. • While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment. • More frequent lipid status evaluation is recommended in situations such as deterioration of diabetes control, use of a new drug known to affect lipid levels, progression of atherothrombotic disease, considerable weight gain, unexpected adverse change in any lipid parameter, development of a new ASCVD risk factor, or convincing new clinical trial evidence or guidelines that suggest stricter lipid goals. • Liver transaminase levels should be measured before and three months after niacin or fibric acid treatment initiation because most liver abnormalities occur within 3 months of treatment initiation. Liver transaminase levels should be measured periodically thereafter (e.g., semiannually or annually). • Creatine kinase levels should be assessed and the statin discontinued, at least temporarily, when an individual reports clinically significant myalgias or muscle weakness on statin therapy.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines:	<u>Top 10 messages to reduce risk of atherosclerotic cardiovascular disease through cholesterol management</u> • In all individuals, emphasize a heart-healthy lifestyle across the life course. • In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or

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AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (2018)[19]	maximally tolerated statin therapy. ○ Clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin. • In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy. Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. • In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. • In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. • In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 to 189 mg/dL (≥1.8 to 4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium (CAC). • Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement four to 12 weeks after statin initiation or dose adjustment, repeated every three to 12 months as needed. <u>Recommendations for Statin Therapy Use in Patients With ASCVD</u> • In patients who are 75 years of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. • In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels. • In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe. • In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost. • In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy. • In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences.

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	• In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. • In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe. • In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (three to five years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events. <u>Recommendations for primary severe hypercholesterolemia (LDL-C ≥190 mg/dL)</u> • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher, maximally tolerated statin therapy is recommended. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher, ezetimibe therapy is reasonable. • In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL, who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL, while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered. • In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. • In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher and who achieve an on-treatment LDL-C level of 130 mg/dL or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. <u>Recommendations for patients with diabetes mellitus</u> • In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. <u>Primary prevention recommendations for adults 40 to 75 years of age with LDL levels 70 to 189 mg/dL</u> • In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more. • For the primary prevention of clinical ASCVD in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL, the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%). • Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision. • In intermediate-risk adults, risk-enhancing factors favor initiation or

Clinical Guideline	Recommendation
	intensification of statin therapy. • In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy. • In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND o If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); o If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥ 55 years of age; o If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy • In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin. • In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Recommendations for older adults</u> • In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL, initiating a moderate-intensity statin may be reasonable. • In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy. • In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL, it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy. <u>Recommendations for children and adolescents</u> • In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity. • In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C. • In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL or higher with a clinical presentation consistent with familial hypercholesterolemia (FH) and who do not respond adequately with three to six months of lifestyle therapy, it is reasonable to initiate statin therapy. • In children and adolescents with a family history of either early CVD or significant hypercholesterolemia, it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age two years to detect FH or rare forms of hypercholesterolemia. • In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia. • In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome. • In children and adolescents without cardiovascular risk factors or family history of

Clinical Guideline	Recommendation
	early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of nine and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities. <u>Recommendations for hypertriglyceridemia</u> • In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides. • In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy. • In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy. • In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL, and especially fasting triglycerides ≥1000 mg/dL), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy. <u>Recommendations for statin safety and statin-associated side effects</u> • A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully. • In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors. • In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and SAMS, is recommended before initiation of treatment. • In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy. • In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss. • In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity. • In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks. • In patients at increased ASCVD risk with severe statin-associated muscle

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	symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit. • Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS. • In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)[20]**	<u>Statin treatment</u> • The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. • For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%. • Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug

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	interactions, and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. • Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. • Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age. • Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. • Creatine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). • Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in

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	individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug). • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic

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	response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. • In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. <u>Non statin safety</u> • Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. • Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. • In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. • To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. • Bile acid sequestrants should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. • A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. • It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks

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	after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. • It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. • Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. • Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. • Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. • If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)**[21]	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD

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	because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile

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	or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the

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	primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2021)**[22]	Drugs • Currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins), fibrates, bile acid sequestrants, selective cholesterol absorption inhibitors (e.g. ezetimibe) and, more recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and bempedoic acid. Response to all therapy varies widely among individuals and therefore monitoring the effect on LDL-C levels is recommended. • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins also lower triglycerides, and may reduce pancreatitis risk. • Statins should be used as the drugs of first choice in patients at increased risk of ASCVD. • Selective cholesterol absorption inhibitors (ezetimibe) should be considered as second-line therapy, either on top of statins when the therapeutic goal is not achieved, or when a statin cannot be prescribed. • Among patients in whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C levels when administered in combination with ezetimibe. • PCSK9 inhibitors also lower triglycerides, raise HDL-C and apolipoprotein A-I, and lower lipoprotein(a), although the relative contributions of these lipid modifications remain unknown. • PCSK9 inhibitors decrease LDL-C by up to 60%, either as monotherapy or in addition to the maximal statin dose or other lipid-lowering therapies (ezetimibe). • Fibrates are used primarily for triglyceride lowering and, occasionally, for increasing HDL-C. Evidence supporting the use of these drugs for CVD event reduction is limited and, given the strong evidence favoring statins, routine use of these drugs in CVD prevention is not recommended. In order to prevent pancreatitis, when triglycerides are >10 mmol/L (>900 mg/dL) they must be reduced not only by drugs but also by restriction of alcohol, treatment of DM, withdrawal of estrogen therapy, etc. In those rare patients with severe primary hypertriglyceridemia, specialist referral must be considered. Recommendations for pharmacological low-density lipoprotein cholesterol lowering for those <70 years of age • It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group. • If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. • For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered. • For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may be considered. • If the goal is not achieved, statin combination with a bile acid sequestrant may be considered.

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American Heart Association/ American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2021)[23]**	Secondary Stroke Prevention • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or transient ischemic attack (TIA) presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other clinical ASCVD. • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, and LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD. • Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2018 ACC/AHA cholesterol guidelines, which include lifestyle modifications, dietary recommendations, and medication recommendations. Treatment of Hypertriglyceridemia • In patients with ischemic stroke or TIA with fasting TG 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL, on moderate or high-intensity statin, with HbA_{1c} <10%, and with no history of pancreatitis, AF, or severe heart failure, treatment with icosapent ethyl (IPE) 2 g twice a day is reasonable to reduce risk of recurrent stroke. • To further reduce the risk of ASCVD in patients with severe hypertriglyceridemia (>500 mg/dL), patients should implement a low-fat diet, avoid refined carbohydrates and alcohol, and consume omega-3 fatty acids.
American Association of the Study of Liver Disease: **Primary Biliary Cholangitis (2018)[24] and Update (2021)[25]**	• Ursodeoxycholic acid (UDCA) at a dose of 13 to 15 mg/kg/day is the first-line therapy for primary biliary cholangitis (PBC). • UDCA is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage. • For patients requiring bile acid sequestrants, UDCA should be given at least one hour before or four hours after the bile acid sequestrant. • Biochemical response to UDCA should be evaluated at 12 months after treatment initiation to determine whether patients should be considered for second-line therapy. • Obeticholic acid (OCA) was approved by the Food and Drug Administration in May 2016 to be used in combination with UDCA in patients with PBC who have inadequate response to at least one year of treatment with UDCA, or as monotherapy for those patients who are intolerant to UDCA. • Patients who are inadequate responders to UDCA should be considered for treatment with OCA, starting at 5 mg/day. • Fibrates can be considered as off-label alternatives for patients with PBC and inadequate response to UDCA, although fibrates are discouraged in patients with decompensated liver disease. • Use of OCA and fibrates is discouraged in patients with decompensated liver disease (Child-Pugh-Turcotte B or C). • OCA is contraindicated in patients with advanced cirrhosis, defined as cirrhosis with current or prior evidence of liver decompensation or portal hypertension. • Cholestyramine, colestipol, and colesevelam are nonabsorbable, highly positively charged resins that bind to negatively charged anions such as bile acids. It is not known which substance in the gut they may be binding to that leads to improved cholestatic itching, and clinical trials proving their efficacy are limited, but they have a long track record of clinical use.
National Institute for Health and Clinical Excellence: **Identification and management of**	Drug treatment in adults • When offering lipid-modifying drug therapy to adults with familial hypercholesterolemia (FH), inform the patient that this treatment should be life-long. • Offer a high-intensity statin to achieve a recommended reduction in LDL-C

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familial hypercholesterolaemia (2008)[26] **Last updated October 2019**	concentration of greater than 50% from baseline. • The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications or intolerance to initial statin therapy. • Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who have been initiated on statin therapy when: o Serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy AND o Consideration is being given to changing from initial statin therapy to an alternative statin. • Appropriate control of cholesterol concentrations should be based on individualized risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. • Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist center. • Offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). • Offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are at a very high risk of a coronary event [i.e., they have established coronary heart disease, a family history of premature coronary heart disease, or two or more other cardiovascular risk factors (e.g. they are male, they smoke, or they have hypertension or diabetes)]. • Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration. • The decision to offer treatment with a bile acid sequestrant (resin) or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH. • Exercise caution when adding a fibrate to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together. <u>Drug treatment in children and young people</u> • All children and young people diagnosed with, or being investigated for, a diagnosis of FH should have a referral to a specialist with expertise in FH in children and young people. • Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of ten years. The decision to defer or offer lipid-modifying drug therapy to a child or young person should take into account their age, the age of onset of coronary heart disease within the family, and the presence of other cardiovascular risk factors, including LCL-C concentration. • When offering lipid-modifying drug therapy for children or young people, inform the child/young person and their parent/caregiver that this treatment should be life-long. • Offer statins to children with FH by the age of ten years or at the earliest opportunity thereafter.

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	• For children and young people with FH, consider a statin that is licensed for use in the appropriate age group.
	• Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group.
	• In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering:
	  ○ A higher dose of statin than is licensed for use in the age group, and/or
	  ○ More than one lipid-modifying drug therapy, and/or
	  ○ Lipid-modifying drug therapy before the age of ten years.
	• In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy, and this should be considered before LDL apheresis.
	• In children and young people with FH who are intolerant of statins, consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration [such as bile acid sequestrants (resins), fibrates, or ezetimibe].
	• Routine monitoring of growth and pubertal development in children and young people with FH is recommended.

American College of Cardiology: **Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2022)**[27]	• Provides recommendations for situations not covered by the 2018 ACC/AHA cholesterol guidelines and for whether or when to use non-statin therapies if response to statins is deemed inadequate. • For all patient groups, lifestyle modification (adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) is a critical component of ASCVD risk reduction. The clinician-patient discussion regarding the addition of a non-statin medication to the current medication regimen should address the potential for net ASCVD risk reduction, safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering, cost, convenience, and medication storage, pill burden, frequency and route of administration, potential to jeopardize adherence to evidence-based therapies and patient preference. <u>Adults With Clinical ASCVD on Statin Therapy for Secondary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider LDL apheresis under care of lipid specialist if baseline LDL-C ≥190 mg/dL not due to secondary causes without clinical or genetic diagnosis of familial hypercholesterolemia. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH under care of lipid specialist, if at very high risk and baseline LDL-C ≥190 mg/dL not due to secondary causes with clinical diagnosis or genetic confirmation of familial hypercholesterolemia. <u>Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Primary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH.
European Atherosclerosis Society/European Society of Vascular Medicine Joint Statement: **Lipid-lowering and**	• Statins, at the highest tolerated dose, are indicated in patients with PAD for the prevention of cardiovascular events. • LCL-C should be lowered to <1.4 mmol/L and by >50% if pre-treatment values are 1.8 to 3.5 mmol/L. • Combination treatment with a statin and ezetimibe may be considered to improve LDL-C goal attainment. This approach could allow better tolerance of a lower dose of statin in patients with statin side-effects.

Clinical Guideline	Recommendation
anti-thrombotic therapy in patients with peripheral arterial disease (2021)[28]	• A PCSK9 inhibitor should be added if LDL-C levels remain 50% higher than goal despite statin treatment, with or without ezetimibe. • Antiplatelet therapy is indicated to prevent further cardiovascular events. This should either be clopidogrel 75 mg/day or the combination of aspirin 100 mg/day and rivaroxaban. • Dual antiplatelet therapy should be given for at least one month after drug coated balloon angioplasty, and for three months after either drug eluting or covered stent implantation. • Combination therapy with aspirin and rivaroxaban should be considered for dual antiplatelet therapy post-intervention.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the HMG-CoA reductase inhibitors are noted in Table 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 4. FDA-Approved Indications for the HMG-CoA Reductase Inhibitors[1-12]

Indications	Single Entity Agents							Combination Products	
	Atorva-statin	Fluva-statin	Lova-statin	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodi-pine and atorvastatin*	Ezetimibe and simva-statin
Hypertriglyceridemia									
Reduce elevated triglycerides (TG) in patients with hypertriglyceridemia							✔		
Treatment of adult patients with hypertriglyceridemia						✔			
Treatment of patients with elevated TG levels	✔				✔			✔ (atorva-statin)	
Primary Hypercholesterolemia and Mixed Dyslipidemia									
Reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and TG and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia and mixed dyslipidemia	✔	✔	✔ § (ER)	✔	✔	✔	✔	✔ (atorva-statin)	✔
Reduce elevated TC, LDL-C, and ApoB in pediatric patients eight years and older with heterozygous familial hypercholesterolemia				✔ (Livalo)					
Reduce TC, LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 (lovastatin only) or 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk factors are present in the pediatric patient	✔ ¶	✔ #	✔ ** (IR)		✔ ††	✔ ‡‡	✔ **	✔ ¶ (atorva-statin)	
Reduce elevated TG and very LDL-C in patients with primary dysbetalipoproteinemia							✔		

Indications	Single Entity Agents							Combination Products	
	Atorva-statin	Fluva-statin	Lova-statin	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodi-pine and atorvastatin*	Ezetimibe and simva-statin
Reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔						✔	✔ (atorva-statin)	✔
Reduce TC, LDL-C, and apo B in adult patients with homozygous familial hypercholesterolemia as adjunctive therapy to other lipid-lowering treatments or alone if such treatments are not available						✔			
Reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments or if such treatments are unavailable									
Reduce LDL-C, TC, non-HDL-C, and ApoB in pediatric patients with homozygous familial hypercholesterolemia, either alone or with other lipid-lowering treatments						✔ §§			
Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia			✔ §						
Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	✔				✔	✔		✔ (atorva-statin)	
Prevention of Cardiovascular Disease									
Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels						✔			
Reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes, and without clinically evidence coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension	✔							✔ (atorva-statin)	
Reduce the risk of myocardial infarction, stroke, and for revascularization procedures and angina in adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart	✔							✔ (atorva-statin)	

Indications	Single Entity Agents							Combination Products	
	Atorva-statin	Fluva-statin	Lova-statin	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodi-pine and atorvastatin*	Ezetimibe and simva-statin
disease									
Reduce the risk of myocardial infarction, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident coronary heart disease					✔				
Reduce the risk of myocardial infarction, unstable angina, and coronary revascularization procedures in patients without symptomatic cardiovascular disease, average to moderately elevated TC and LDL-C, and below average HDL-C			✔						
Reduce the risk of non-fatal myocardial infarction, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evidence coronary heart disease	✔							✔ (atorvastatin)	
Reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in patients without clinically evidence coronary heart disease but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease						✔			
Reduce the risk of total mortality by reducing coronary death, myocardial infarction, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evidence coronary heart disease					✔				
Reduce the risk of total mortality by reducing coronary heart disease deaths, non-fatal myocardial infarction and stroke, and need for coronary and non-							✔		

Indications	Single Entity Agents							Combination Products	
	Atorva-statin	Fluva-statin	Lova-statin	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodi-pine and atorvastatin*	Ezetimibe and simva-statin
coronary revascularization procedures in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease									
Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evidence coronary heart disease		✔							
Slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower TC and LDL-C to target levels			✔						
Other									
Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease by angiography and without heart failure or an ejection fraction <40%								✔ (amlodi-pine)	
Symptomatic treatment of chronic stable angina								✔ (amlodi-pine)	
Treatment of confirmed or suspected vasospastic angina								✔ (amlodi-pine)	
Treatment of hypertension								✔ (amlodi-pine)	

*Indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.
§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
‖When the response to an appropriate diet has been inadequate.
¶In boys and postmenarchal girls 10 to 17 years of age.
#In adolescent boys and adolescent girls who are at least one year post-menarche, 10 to 16 years of age.
**In adolescent boys and girls, who are at least one year post-menarche, 10 to 17 years of age.
††In children and adolescent patients ages eight years of age and older.
‡‡ In children and adolescents 8 to 17 years of age.
§§ In children and adolescents 7 to 17 years of age.
ER=extended-release, IR=immediate-release.

IV. Pharmacokinetics

The pharmacokinetic parameters of the HMG-CoA reductase inhibitors are listed in Table 5. All statins undergo extensive first-pass metabolism, resulting in relatively low bioavailability following oral administration. However, the hepatic HMG-CoA inhibition occurs as a result of the high liver concentrations during first-pass metabolism. Thus, their therapeutic effect is not lessened by this high first-pass extraction.[12,13]

Table 5. Pharmacokinetic Parameters of the HMG-CoA Reductase Inhibitors[13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Atorvastatin	14	98	Liver (significant; % not reported)	Renal (1 to 2) Bile (primary; % not reported)	7 to 14
Fluvastatin	20 to 30	98	Liver (% not reported)	Renal (5) Bile (95) Feces (95)	<3
Lovastatin	5	>95	Liver (extensive; % not reported)	Renal (10) Feces (83)	Not reported
Pitavastatin	51*	99	Liver (extensive; % not reported)	Renal (15) Bile (extensive; % not reported) Feces (79)	11 to 12
Pravastatin	17	43 to 55	Liver (extensive; % not reported)	Renal (20) Feces (71)	2.6 to 3.2
Rosuvastatin	20	88	Liver (minimal; % not reported)	Renal (10) Feces (90)	19
Simvastatin	5	95	Liver (extensive; % not reported)	Renal (13) Feces (60)	Not reported
Combination Products					
Amlodipine and atorvastatin	AM: 64 to 90 AT: 14	AM: 93 AT: 98	AM: Liver (extensive; % not reported) AT: (significant; % not reported)	AM: Renal (70) AT: Renal (1 to 2) Bile (primary; % not reported)	AM: 30 to 60 AT: 7 to 14
Ezetimibe and simvastatin	E: not reported S: 5	E: >90 S: 95	E: Liver (% not reported) Small intestine (extensive; % not reported) S: Liver (extensive; % not reported)	E: Renal (11) Feces (78) S: Renal (13) Feces (60)	E: 19 to 30 S: not reported

*Oral solution.
AM=amlodipine, AT=atorvastatin, E=ezetimibe, S=simvastatin

V. Drug Interactions

Major drug interactions with the HMG-CoA reductase inhibitors are listed in Table 6.

Table 6. Major Drug Interactions with the HMG-CoA Reductase Inhibitors[13]

Generic Name(s)	Interaction	Mechanism
Amlodipine	Simvastatin	The mechanism of interaction is unknown. Simvastatin plasma concentrations may be elevated, increasing the risk of toxicity.
HMG-CoA reductase	Amiodarone	Inhibition of cytochrome P450 isoenzymes by amiodarone may

Generic Name(s)	Interaction	Mechanism
inhibitors (atorvastatin, lovastatin, simvastatin)		decrease the metabolic elimination of HMG-CoA reductase inhibitors. The pharmacologic effects of HMG-CoA reductase inhibitors may be increased by amiodarone. Elevated plasma concentrations with toxicity characterized by muscle injury may occur.
HMG-CoA reductase inhibitors (fluvastatin, lovastatin, rosuvastatin, simvastatin)	Anticoagulants	The hypoprothrombinemic effects of anticoagulants may be increased HMG-CoA reductase inhibitors. Hematuria, epistaxis and rectal bleeding may occur. The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)	Azole antifungals	Azole antifungals may inhibit first-pass hepatic metabolism of HMG-CoA reductase inhibitors, increasing plasma levels and adverse reactions of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Carbamazepine	Induction of CYP3A4 metabolism by carbamazepine may cause increased metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be decreased by carbamazepine.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	Cyclosporine	Cyclosporine may decrease the elimination of HMG-CoA reductase inhibitors by inhibiting their metabolism. Toxic effects of HMG-CoA reductase inhibitors including liver enzyme elevation, myopathy, and rhabdomyolysis may be increased by cyclosporine.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Delavirdine	Delavirdine inhibits HMG-CoA reductase metabolism, increasing HMG-CoA reductase inhibitor plasma concentrations and increasing the risk of severe myopathy or rhabdomyolysis.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Diltiazem	The inhibition of cytochrome P450 (CYP) 3A4 isoenzymes by diltiazem may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by co-administration of diltiazem. The risk of myopathy and rhabdomyolysis may be increased.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, simvastatin)	Efavirenz	Induction of CYP3A4 isoenzymes by efavirenz may increase the metabolic elimination of HMG-CoA reductase inhibitors. Efavirenz may decrease plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	Fibric acid derivatives	Coadministration of fibric acid derivatives with HMG-CoA reductase inhibitors may result in myopathy or rhabdomyolysis.
HMG-CoA reductase	Hepatitis C virus	HCV protease inhibitors may inhibit the metabolism of HMG-

Generic Name(s)	Interaction	Mechanism
inhibitors (all)	(HCV) protease inhibitors	CoA reductase inhibitors, increasing plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Imatinib	Inhibition of CYP3A4 isoenzymes by imatinib may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by imatinib.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Macrolides and related antibiotics	Inhibition of CYP3A4 isoenzymes by macrolides and ketolides may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Macrolides and ketolides may increase pharmacologic effects of HMG-CoA reductase inhibitors. Elevated plasma concentrations with toxicity characterized by liver enzyme elevation and myopathy may occur.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Mifepristone	Mifepristone may inhibit the metabolism of HMG-CoA reductase inhibitors, increasing HMG-CoA reductase inhibitor plasma concentrations and pharmacologic effects.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Nefazodone	Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of HMG-CoA reductase inhibitors. The risk of myopathy and rhabdomyolysis may be increased when HMG-CoA reductase inhibitors and nefazodone are coadministered.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, simvastatin)	Non-nucleoside reverse transcriptase inhibitors (NNRT inhibitors)	Inhibition of CYP3A4 isoenzymes by NNRT inhibitors may decrease the metabolic elimination of HMG-CoA reductase inhibitors. NNRT inhibitors may increase plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (rosuvastatin)	Protease inhibitors	Inhibition of CYP3A4 isoenzymes by protease inhibitors may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Pharmacologic and toxic effects of HMG-CoA reductase inhibitors may be increased by protease inhibitors.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Ranolazine	Ranolazine inhibits the metabolism of HMG-CoA reductase inhibitors, increasing HMG-CoA reductase inhibitor plasma concentrations and increasing the risk of adverse events.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)	Rifamycins	Induction of pre-hepatic and hepatic CYP3A4-mediated metabolism by rifamycins may increase the metabolic elimination of HMG-CoA reductase inhibitors. Pharmacologic effects of HMG-CoA reductase inhibitors may be decreased by rifamycins and impaired cholesterol-lowering efficacy may result.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Verapamil	Inhibition of CYP3A4 isoenzymes by verapamil may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by verapamil. Toxicity, characterized by muscle injury, may occur.
Ezetimibe	Cyclosporine	When cyclosporine and ezetimibe are co-administered, exposure to both drugs may be increased potentially increasing the pharmacologic effects and adverse reactions. The mechanism of this interaction is unknown.

VI. Adverse Drug Events

The most common adverse drug events reported with the HMG-CoA reductase inhibitors are listed in Table 7. These agents are generally well tolerated with only mild side effects, such as abdominal pain, constipation, flatulence, and headache. Myopathy has also been reported with the HMG-CoA reductase inhibitors, which can progress to rhabdomyolysis and acute renal failure. Risk factors for developing rhabdomyolysis include age >65 years, hypothyroidism, and poor renal function. Increases in hepatic transaminases greater than three times the upper limit of normal have also been reported with the HMG-CoA reductase inhibitors.[1-13]

Table 7. Adverse Drug Events (%) Reported with the HMG-CoA Reductase Inhibitors[1-13]

Adverse Event	Single Entity Agents							Combination Products	
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin
Cardiovascular									
Angina pectoris	<2	-	-	-	3.1	-	-	-	-
Arrhythmia	<2	-	-	-	0.1 to 2.6	-	-	<2/✔	-
Bradycardia	-	-	-	-	-	-	-	-/✔	-
Chest pain	≥2	-	0.5 to 1.0	-	-	-	-	≥2.0/✔	-
Hypertension	<2	-	-	-	-	-	-	-	-
Hypotension	-	-	-		-	-	-	-/✔	-
Migraine	<2	-	-	-	-	-	-	-	-
Palpitation	<2	-	-	-	-	-	-	<2/0.7 to 4.5	-
Peripheral ischemia	-	-	-		-	-	-	✔/-	-
Postural hypotension	<2	-	-	-	-	-	-	<2/✔	-
Syncope	<2	-	-	-	-	-	-	<2/✔	-
Tachycardia	-	-	-	-	-	-	-	-/✔	-
Vasodilatation	<2	-	-	-	-	-	-	-/✔	-
Central Nervous System/Neurological									
Abnormal dreams	<2	-	-	-	-	-	-	<2/✔	-
Amnesia	<2	-	-	-	-	-	-	-	-
Anxiety	-	✔	✔	-	1	-	✔	-/✔	-
Chills	-	✔	✔	-	✔	-	✔	-	-
Cranial nerve dysfunction	-	✔	✔	-	✔	-	✔	-	-
Depersonalization	-	-	-	-	-	-	-	-/✔	-
Depression	<2	✔	✔	-	1	-	✔	<2/✔	-
Dizziness	≥2	✔	0.5 to 1.2/2.0	-	1.0 to 2.2	≤4	✔	≥2.0/1.1 to 3.4	-
Emotional lability	<2	-	-	-	-	-	-	-	-
Facial paralysis/paresis	<2	✔	-	-	✔	-	✔	-	-
Fever	<2	✔	-	-	<1	-	✔	-	-
Flushing	-	✔	✔	-	<1	-	✔	-/0.7 to 4.5	-
Headache	2.5 to 16.7	8.9/4.7	✔	✔	1.7 to 1.9	3.1 to 8.5	3.5	2.5 to 16.7/7.3	5.8
Hyperkinesia	<2	-	-	-	-	-	-	-	-
Hypertonia	<2	-	-	-	-	-	-	-	-
Hypesthesia	<2	-	-	-	-	-	-	-/✔	-
Impairment of extraocular movement	-	✔	-	-	✔	-	-	-	-
Incoordination	<2	-	-	-	-	-	-	-	-
Insomnia	≥2	2.7/0.8	0.5 to 1.0	-	1	-	✔	≥2/✔	-

Adverse Event	Single Entity Agents							Combination Products	
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin
Libido decreased	<2	✔	✔	-	<1	-	✔	-	-
Memory loss	-	✔	✔	-	<1	✔	✔	-	-
Neck rigidity	<2	-	-	-	-	-	-	-	-
Nervousness	-	-	-	-	-	-	-	-/✔	-
Paresthesia	<2	✔	0.5 to 1.0/-	-	<1	-	✔	<2/✔	-
Peripheral nerve palsy	-	✔	✔	-	<1	-	✔	-	-
Peripheral neuropathy	<2	✔	✔	-	<1	-	✔	-	-
Psychiatric disturbances	-	✔	✔	-	<1	-	✔	<2/✔	-
Somnolence	<2	-	-	-	-	-	-	<2.0/1.3 to 1.6	-
Tremor	-	✔	✔	-	<1	-	✔	-/✔	-
Vertigo	-	✔	✔	-	<1	-	✔	-/✔	-
Dermatological									
Acne	<2	-		-	-	-	-	-	-
Alopecia	<2	✔	0.5 to 1.0/-	-	<1	-	✔	-	-
Contact dermatitis	<2	-	-	-	-	-	-	-	-
Dry skin	<2	✔	✔	-	<1	-	✔	-	-
Eczema	<2	-	-	-	-	-	0.8	-	-
Erythema multiforme	<2	✔	✔	-	✔	-	✔	<2/✔	-
Pruritis	<2	✔	0.5 to 1.0/-	-	<1	<2	0.5	<2/✔	-
Rash	1.1 to 3.9	✔	0.8 to 1.3/-	-	1.3 to 2.1	<2	0.6	<2/✔	-
Rash erythematous	-	-	-	-	-	-	-	-/✔	-
Rash maculopapular	-	-	-	-	-	-	-	-/✔	-
Seborrhea	<2	-	-	-	-	-	-	-	-
Skin ulcer	<2	-	✔	-	-	-	-	-	-
Stevens-Johnson syndrome	✔	✔	-	-	✔	-	✔	-	-
Sweating	<2	-	-	-	-	-	-	<2/✔	-
Toxic epidermal necrolysis	✔	✔	✔	-	✔	-	✔	-	-
Urticaria	<2	✔	✔	-	-	<2	-	-	-
Endocrine and Metabolic									
Gout	<2	-	-	-	-	-	-	-	-
Hyperglycemia	<2	✔	-	-	-	-	-	<2/✔	-
Hypoglycemia	<2	-	-	-	-	-	-	-	-
Peripheral edema	≥2	-	-	-	-	-	-	<2/✔	-
Thirst	-	-	-	-	-	-	-	-/✔	-
Weight decrease	-	-	-	-	-	-	-	-/✔	-
Weight gain	<2	-	-	-	-	-	-	<2/✔	-
Gastrointestinal									
Abdominal pain	0.0 to 3.8	4.9/3.7	2.0 to 2.5/-	-	2.0 to 2.4	≤2.4	0.9 to 3.2	0 to 3.8/1.6	-
Acid regurgitation	-	-	0.5 to 1.0/-	-	-	-	-	-	-
Anorexia	<2	✔	✔	-	-	-	✔	0 to 3.8/1.6	-
Biliary pain	<2	-	-	-	-	-	-	-	-
Cheilitis	<2	-	-	-	-	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products	
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin
Cholecystitis	-	-	-	-	-	-	-	-	-
Cholestatic jaundice	<2	✔	✔	-	✔	✔	✔	-	-
Cirrhosis	-	✔	✔	-	✔	-	✔	-	-
Colitis	<2	-	-	-	-	-	-	-	-
Constipation	0 to 2.5	-	2.0 to 3.5/-	1.5 to 3.6	1.2 to 2.4	2.1 to 4.7	2.3	0 to 2.5/✔	-
Decreased appetite	-	-	-	-	<1	-	-	-	-
Diarrhea	0 to 5.3	4.9/3.3	2.2 to 2.6 to 3.0	1.5 to 2.6	2	-	0.5 to 1.9	0 to 5.3/✔	2.8
Dry mouth	<2	-	0.5 to 1.0/-	-	-	-	-	<2/✔	-
Duodenal ulcer	<2	-	-	-	-	-	-	-	-
Dyspepsia/heartburn	1.3 to 2.8	7.9/3.5	1.0 to 1.6/-	-	2.0 to 3.5	-	0.6 to 1.1	1.3 to 2.8/✔	-
Dysphagia	<2	-	-	-	-	-	-	<2/✔	-
Enteritis	<2	-	-	-	-	-	-	-	-
Eructation	<2	-	-	-	-	-	-	-	-
Esophagitis	<2	-	-	-	-	-	-	-	-
Flatulence	1.1 to 2.8	2.6/1.4	3.7 to 4.5	-	1.2 to 2.7	-	0.9 to 1.9	1.1 to 2.8/✔	-
Fulminant hepatic necrosis	-	✔	✔	-	✔	-	✔	-	-
Gastritis	<2	-	-	-	-	-	-	-	-
Gastroenteritis	<2	-	-	-	-	-	-	-	-
Gingival hyperplasia	-	-	-	-	-		-	-/✔	-
Glossitis	<2	-	-	-	-	-	-	-	-
Gum hemorrhage	<2	-	-	-	-	-	-	-	-
Hepatitis	<2	✔	✔	-	✔	✔	✔	-	-
Hepatoma	-	✔	✔	-	✔	-	✔	-	-
Increased appetite	<2	-	-	-	-	-	-	-	-
Melena	<2	-	-	-	-	-	-	-	-
Mouth ulceration	<2	-	-	-	-	-	-	-	-
Nausea	≥2	3.2/2.5	-	-	1.6 to 2.9	0 to 6.3	0.4 to 1.3	≥2.0/2.9	-
Pancreatitis	<2	✔	✔	-	✔	<2	✔	<2/✔	-
Rectal hemorrhage	<2	-	-	-	-	-	-	-	-
Stomach ulcer	<2	-	-	-	-	-	-	-	-
Stomatitis	<2	-	-	-	-	-	-	-	-
Tenesmus	<2	-	-	-	-	-	-	-	-
Ulcerative stomatitis	<2	-	-	-	-	-	-	-	-
Vomiting	<2	✔	0.5 to 1.0/-	-	1.6 to 2.9	-	✔	<2/✔	-
Genitourinary									
Abnormal ejaculation	<2	-	-	-	-	-	-	-	-
Albuminuria	≥2	-	-	-	-	-	-	-	-
Breast enlargement	<2	-	-	-	-	-	-	-	-
Cystitis	<2	-	-	-	-	-	-	-	-
Dysuria	<2	-	-	-	<1	-	-	-	-
Epididymitis	<2	-	-	-	-	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products	
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin
Erectile dysfunction	-	✔	✔	-	<1	-	✔	-	-
Fibrocystic breast	<2	-	-	-	-	-	-	-	-
Gynecomastia	-	✔	✔	-	✔	-	✔	-	-
Hematuria	≥2	-	-	-	-	-	-	-	-
Impotence	<2	-	-	-	-	-	-	-	-
Kidney calculus	<2	-	-	-	-	-	-	-	-
Metrorrhagia	<2	-	-	-	-	-	-	-	-
Nephritis	<2	-	-	-	-	-	-	-	-
Nocturia	<2	-	-	-	<1	-	-	<2/✔	-
Urinary abnormality	-	-	-	-	0.7 to 1.0	-	-	-/✔	-
Urinary frequency	<2	-	-	-	<1	-	-	<2/✔	-
Urinary incontinence	<2	-	-	-	-	-	-	-	-
Urinary retention	<2	-	-	-	-	-	-	-	-
Urinary tract infection	≥2	1.6/2.7	-/2	-	-	-	-	-	-
Urinary urgency	<2	-	-	-	1	-	-	-	-
Uterine hemorrhage	<2	-	-	-	-	-	-	-	-
Vaginal hemorrhage	<2	-	-	-	-	-	-	-	-
Hematologic									
Anemia	<2	-	-	-	-	-	-	-	-
Ecchymosis	<2	-	-	-	-	-	-	-	-
Eosinophilia	-	✔	✔	-	✔	-	✔	-	-
Hemolytic anemia	-	✔	✔	-	✔	-	✔	-	-
Leukopenia	-	✔	✔	-	✔	-	-	-/✔	-
Lymphadenopathy	<2	-	-	-	-	-	-	-	-
Petechia	<2	-	-	-	-	-	-	-	-
Prolongation of prothrombin time	-	-	-	-	-	-	-	-	-
Purpura	-	✔	✔	-	✔	-	✔	-/✔	-
Thrombocytopenia	<2	✔	✔	-		-	✔	2/✔	-
Vasculitis	-	✔	✔	-	✔	-	✔	-/✔	-
Laboratory Test Abnormalities									
γ-glutamyl transpeptidase increase	-	-	-	-	-	-	-	-	-
Abnormal thyroid function tests	-	-	-	-	-	-	-	-	-
Bilirubin elevation	-	✔	✔	✔	-	✔	✔	-	-
Creatine phosphokinase increased	<2	-	-	✔	-	2.6	✔	-	-
Eosinophil sedimentation rate increase	-	✔	✔	-	✔	-	✔	-	-
Fasting glucose increase	-	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	-	✔	-	-	-
Hyperkalemia									
Lactate dehydrogenase decrease	-	-	-	-	-	-	-	-	-
Liver enzyme abnormalities	-	✔	✔	✔	✔	2.2	✔	-	0.4 to 3.7
Phosphorus decrease	-	-	-	-	-	-	-	-	-
Positive antinuclear antibody	-	✔	✔	-	✔	-	✔	-	-
Proteinuria	-	-	-	-	-	✔	-	-	-
Thyroid level abnormality	-	✔	✔	-	✔	✔	✔	-	-

Adverse Event	Single Entity Agents							Combination Products	
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin
Uric acid increase	-	-	-	-	-	-	-	-	-
Musculoskeletal									
Arthralgia	0 to 5.1	-/3.2	0.5 to 1.5/5.0	✔	6	10.1	✔	0 to 5.1/✔	-
Arthritis	≥2	2.1/1.3	0.5 to 6.0/5.0	-	✔	-	✔	-/✔	-
Back pain	0 to 3.8	-	-/5	1.4 to 3.9	-	-	-	0 to 3.8/✔	0.4
Bursitis	<2	-	-	-	-	-	-	-	-
Dermatomyositis	-	-	-	-	✔	-	-	-	-
Immune-mediated necrotizing myopathy	-	-	-	-	-	-	-	-	-
Leg cramps	<2	-	0.5 to 1.0/-	-	-	-	-	-	-
Leg pain	-	-	-	-	-	-	-	-	-
Localized pain	-	-	-	-	1.4	-	-	-	-
Muscle cramps	-	✔	0.6 to 1.1/-	-	2	-	✔	-/✔	-
Myalgia	0 to 5.6	5.0/3.8	1.8 to 3.0/3.0	1.9 to 3.1	0.6 to 1.4	1.9 to 12.7	1.2	0 to 5.6/✔	0.6 to 3.6
Myopathy	-	✔	-	-	✔	-	✔	-	-
Myositis	<2	-	-	-	-	-	-	-	-
Myasthenia	<2	-	-	-	<1	-	-	-	-
Pain in extremity	-	-	-	0.6 to 2.3	-	-	-	-	2.3
Polymyalgia rheumatica	-	✔	✔	-	✔	-	✔	-	-
Rhabdomyolysis	✔	✔	✔	-	✔	-	✔	-	-
Shoulder pain	-	-	0.5 to 1.0/-	-	-	-	-	-	-
Tendinous contracture	<2	-	-	-	-	-	-	-	-
Tendon rupture									
Tenosynovitis	<2	-	-	-	-	-	-	-	-
Respiratory									
Asthma	<2	-	-	-	-	-	-	-	-
Bronchitis	≥2	1.2/2.6	-	-	-	-	-	-	-
Cough	-	-	-	-	0.1 to 1.0	-	-	-	-
Dyspnea	<2	✔	✔	-	1.6	-	✔	<2/✔	-
Epistaxis	<2	-	-	-	-	-	-	<2/✔	-
Pharyngitis	0 to 2.5	-	-	-	-	-	-	-	-
Pneumonia	<2	-	-	-	-	-	-	-	-
Rhinitis	≥2	-	-	-	0.1	-	-	-	-
Sinusitis	0 to 6.4	2.6/3.5	-/4	-	-	-	-	-	-
Upper respiratory infection	-	-	-	-	1.3	-	2.1	-	3.6
Other									
Abnormal vision	-	-	-	-	-	-	-	-/✔	-
Accidental injury	0 to 4.2	5.1/4.2	-/6	-	-	-	-	0 to 2.8/✔	-
Allergic reaction	0 to 2.8	2.3/1.0	-	-	<1	-	-	-	-
Amblyopia	<2	-	-	-	-	-	-	-	-
Anaphylaxis	✔	✔	✔	-	✔	-	✔	-	-
Angioedema	-	✔	✔	-	✔	<2	✔	-/✔	-
Angioneurotic edema	✔	-	-	-	-	-	-	-	-
Asthenia	0 to 3.8	✔	1.2 to 2.0/3.0	-	✔	0.9 to 4.7	1.6	0 to 3.8/✔	-
Blurred vision	-	-	0.9 to 1.2/-	-	-	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products	
	Atorvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Pitavastatin	Pravastatin	Rosuvastatin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin
Cataracts	-	✔	✔	-	-	-	0.5	-	-
Conjunctivitis	-	-	-	-	-	-	-	-/✔	-
Deafness	<2	-	-	-	-	-	-	-	-
Diplopia	-	-	-	-	-	-	-	-/✔	-
Dry eyes	<2	-	-	-	-	-	-	-	-
Eye hemorrhage	<2	-	-	-	-	-	-	-	-
Eye irritation	-	-	0.5 to 1.0/-	-	-	-	-	-	-
Eye pain	-	-	-	-	-	-	-	-/✔	-
Facial/general edema	<2	-	-	-	<1	-	-	-	-
Fatigue	✔	2.7/1.6	-	-	1.9 to 3.4	-	-	✔/4.5	-
Flu syndrome	0 to 3.2	5.1/7.1	-/5	-	-	-	-	-	-
Glaucoma	<2	-	-/11	-	-	-	-	-	-
Hot flashes	-	-	-	-	-	-	-	-/✔	-
Infection	2.8 to 10.3	-	-	-	-	-	-	-	-
Influenza	-	-	-	✔	-	-	-	-	2.3
Lupus erythematosus-like syndrome	-	✔	✔	-	✔	-	✔	-	-
Malaise	<2	✔	✔	-	✔	-	✔	-	-
Nasopharyngitis	-	-	-	✔	-	-	-	-	-
Ophthalmoplegia	-	✔	✔	-	-	-	✔	-	-
Pain	-	-	-/3	-	-	-	-	-	-
Parosmia	<2	-	-	-	-	-	-	-	-
Photosensitivity reaction	<2	✔	-	-	✔	-	-	-	-
Refraction disorder	<2	-	-	-	-	-	-	-	-
Rigors	-	-	-	-	-	-	-	-/✔	-
Sexual dysfunction	-	-	-	-	-	-	-	-	-
Taste disturbance	<2	✔	-	-	✔	-	-	-/✔	-
Tinnitus	<2	-	-	-	-	-	-	<2/✔	-
Visual disturbances	-	-	✔	-	✔	-	-	-	-

✔ Percent not specified.
- Event not reported.
ER=extended-release, IR=immediate-release

VII. Dosing and Administration

The usual dosing regimens for the HMG-CoA reductase inhibitors are listed in Table 8. All statins are dosed once daily with the exception of maximum doses of lovastatin and fluvastatin immediate-release products, which should be divided into twice daily dosing. Atorvastatin, rosuvastatin, and fluvastatin extended-release formulation are the only statins that may be administered at any time in the day. The other statins should be administered in the evening or at bedtime to target the time of maximum cholesterol synthesis.[1-12]

Table 8. Usual Dosing Regimens for the HMG-CoA Reductase Inhibitors[1-12]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Atorvastatin	Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia: Suspension, tablet: initial, 10 to 20 mg once daily; maintenance, 10 to 80 mg once daily	Familial hypercholesterolemia in children 10 to 17 years of age: Suspension, tablet: initial, 10 mg/day; maximum, 20 mg/day Safety and efficacy in children <10 years of age have not been established.	Tablet: 10 mg 20 mg 40 mg 80 mg Suspension: 20 mg/ 5 mL
Fluvastatin	Prevention of cardiovascular disease: Capsule, extended-release tablet: 20 to 80 mg/day Primary hypercholesterolemia and mixed dyslipidemia: Capsule: initial, 40 mg once daily or 40 mg twice daily Extended-release tablet: initial, 80 mg once daily	Heterozygous familial hypercholesterolemia in children 10 to 16 years of age: Capsule: initial, 20 mg once daily; maximum, 40 mg twice daily Extended-release tablet: maximum, 80 mg once daily Safety and efficacy in children <9 years of age have not been established.	Capsule: 20 mg 40 mg Extended-release tablet: 80 mg
Lovastatin	Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia: Extended-release tablet: 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day administered in a single or two divided doses; maximum, 80 mg/day	Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Tablet: 10 to 40 mg/day; maximum, 40 mg/day Safety and efficacy in children have not been established (extended-release tablet). Safety and efficacy in pre-pubertal patients or children <10 years of age have not been established (tablet).	Extended-release tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg
Pitavastatin	Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 2 mg once daily; maintenance, 1 to 4 mg once daily; maximum, 4 mg/day	Heterozygous familial hypercholesterolemia in children 8 years of age and older: Tablet (Livalo®): initial, 2 mg once daily; maintenance, 1 to 4 mg once daily; maximum, 4 mg/day	Tablet (pitavastatin calcium, Livalo®): 1 mg 2 mg 4 mg Tablet

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
			(pitavastatin magnesium, Zypitamag®): 2 mg 4 mg
Pravastatin	Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily	Heterozygous familial hypercholesterolemia in children >8 to 13 years of age: Tablet: initial, 20 mg once daily Heterozygous familial hypercholesterolemia in children 14 to 18 years of age: Tablet: initial, 40 mg once daily Safety and efficacy in children <8 years of age have not been established.	Tablet: 10 mg 20 mg 40 mg 80 mg
Rosuvastatin	Hypertriglyceridemia /Prevention of cardiovascular disease /Primary hypercholesterolemia and mixed dyslipidemia: Sprinkle capsule, tablet: initial, 10 to 20 mg once daily; maintenance, 5 to 40 mg once daily	Heterozygous familial hypercholesterolemia in children 8 to <10 years of age: Tablet: maintenance, 5 to 10 mg/day Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Tablet: maintenance, 5 to 20 mg/day Homozygous familial hypercholesterolemia in children 7 to 17 years of age: Tablet: maintenance, 20 mg/day	Sprinkle capsule: 5 mg 10 mg 20 mg 40 mg Tablet: 5 mg 10 mg 20 mg 40 mg
Simvastatin	Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 10 to 40 mg once daily; 5 to 40 mg/day	Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Tablet: initial, 10 mg once daily; maintenance, 10 to 40 mg/day; maximum, 40 mg/day Safety and efficacy in pre-pubertal patients or children <10 years of age have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg
Combination Products			
Amlodipine and atorvastatin	Hypertension/Coronary artery disease (amlodipine): Tablet: initial, 5 mg once daily; maximum, 10 mg once daily Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia (atorvastatin):	Safety and efficacy in children have not been established.	Tablet: 2.5-10 mg 2.5-20 mg 2.5-40 mg 5-10 mg 5-20 mg 5-40 mg 5-80 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 10 to 20 mg once daily; maintenance, 10 to 80 mg once daily		10-10 mg 10-20 mg 10-40 mg 10-80 mg
Ezetimibe and simvastatin	Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 10-10 or 10-20 mg once daily; maintenance, 10-10 to 10-40 mg/day	Safety and efficacy in children have not been established.	Tablet: 10-10 mg 10-20 mg 10-40 mg 10-80 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the HMG-CoA reductase inhibitors are summarized in Table 9.

Table 9. Comparative Clinical Trials with the HMG-CoA Reductase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Single-entity Agents				
Familial Hypercholesterolemia (Single-Entity Agents)				
Harada-Shiba et al.[29] (2018) Japanese study: Pitavastatin 1 mg vs pitavastatin 2 mg European study: Pitavastatin 1, 2, or 4 mg vs placebo	DB, MC, RCT Japanese study: Japanese boys 10 to 15 years of age with clinically diagnosed heterozygous FH European study: European children 6 to 17 years of age with high risk dyslipidemia (mutations associated with FH in 103 patients out of 106 randomized patients)	Japanese study: N=14 52 weeks European study: N=103 12 weeks (followed by 52 weeks OL extension)	Primary: Percentage change in the LDL-C levels from baseline to week 12 Secondary: Safety	Primary: LDL-C levels were reduced by 28.5 and 36.3% in the 1- and 2-mg groups, respectively in the Japanese study, which was numerically higher than in the European study (23.5 and 30.1%, respectively). Then, using the combined dataset, baseline LDL-C, age, and body weight were identified as factors affecting the percentage LDL-C change based on the pre-specified criterion of P<0.2. Including these identified factors into the model, the LDL-C reductions with pitavastatin 1 and 2 mg from the two studies were adjusted for these factors. As a result, there was no significant difference in the percentage LDL-C reduction in the Japanese study (24.5 and 33.5% in the 1- and 2-mg groups, respectively) compared with the European study (23.6 and 30.8% in the 1- and 2-mg groups, respectively). Secondary: Pitavastatin was well tolerated without any difference in the frequency or nature of adverse events between the treatment groups, or between the studies.
Rodenburg et al.[30] (2007) Pravastatin 20 mg (children <14 years of age) or pravastatin 40 mg (children ≥14 years of age)	FU Children diagnosed with FH, between 8 and 18 years of age, on a fat-restricted diet ≥3 months, with LDL-C ≥4.0 mmol/L and triglyceride levels <4.0	N=214 2 years (mean duration of total treatment with a statin was 4.5 years)	Primary: Percentage change in TC, LDL-C, TG, HDL-C, predictors of smaller carotid IMT, and safety Secondary: Not reported	Primary: Statin therapy was associated with a 22.5% reduction in TC from baseline. Statin therapy was associated with a 29.2% reduction in LDL-C from baseline. Statin therapy was associated with a 3.1% increase in HDL-C from baseline. Statin therapy was associated with a 1.9% reduction in TG from baseline. The study found several independent predictors of smaller carotid IMT:IMT at statin initiation (P<0.001), age at statin initiation (P=0.016), male sex

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	mmol/L on 2 different occasions, using adequate contraception, not on any treatment for hypercholesterolemia, including plant sterol or stanol products			(P<0.001), and the duration of statin therapy (P<0.001). Secondary: Not reported
Kusters et al.[31] (2014) Pravastatin 20 to 40 mg/day During follow-up several patients switched to other statins	FU Children diagnosed with HeFH, between 8 and 18 years of age enrolled in Rodenburg et al. (above)	N=214 10 years	Primary: CIMT; safety Secondary: Not reported	Primary: Ten-year follow-up was achieved in 194 (91%) patients with FH and 83 (87%) siblings. After 10 years, mean CIMT was still significantly greater in patients with FH compared with siblings (0.480 mm vs 0.469 mm, respectively; P=0.02). Progression of CIMT from baseline was similar in both groups (patients with FH, 0.039 mm vs siblings, 0.037 mm; P=0.52). Safety parameters did not differ between patients with FH and siblings. Secondary: Not reported
Avis et al.[32] (2010) PLUTO Rosuvastatin 5, 10 or 20 mg/day for 12 weeks vs placebo All patients were randomized after a 6-week diet lead in period.	DB, MC, PC, RCT Children 10 to 17 years of age with a heFH by documentation of a genetic defect or by predefined clinical criteria, Tanner stage ≥11, with female patients being ≥1 year post menarche and fasting LDL-C ≥190 or >160 mg/dL if there was	N=177 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Changes from baseline in lipoproteins, proportion of patients achieving LDL-C goal (<110 mg/dL), safety	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to placebo (38, 45 and 50 vs 1%; P<0.001 for all). Secondary: Compared to placebo, significant reductions with rosuvastatin were achieved for TC (P<0.001 for all) and apo B (P<0.001), but not for TG (P=0.8, P=0.1 and P=0.1). HDL-C (P=0.4, P=0.2 and P=0.5) and apo AI (P=0.7, P=0.3 and P=0.6) were not significantly different from placebo. No patient receiving placebo achieved the LDL-C goal compared to 12, 41 and 41% of patients receiving rosuvastatin 5, 10 and 20 mg during the DB phase. In the OL phase, the goal was achieved by 40% of patients. A LDL-C goal of <130 mg/dL was achieved by 68% of patients in the OL phase. At the end of the OL phase, 26 patients were receiving rosuvastatin 5 mg, 25 patients were receiving 10 mg and 122 patients were receiving 20 mg.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
After 12 weeks, patients entered a 40 week, OL, dose-titration phase. Patients originally randomized to placebo and those with LDL-C <100 mg/dL on their assigned rosuvastatin dose began the OL phase on rosuvastatin 5 mg/day. All others continued their rosuvastatin dose from the DB phase.	a family history of premature cardiovascular disease or if the patient had ≥2 other risk factors for cardiovascular disease			During the DB phase, the overall frequencies of adverse events were 50, 64, 55 and 54% (P value not reported). The most commonly reported adverse events included nasopharyngitis, influenza, myalgia and nausea. One serious adverse event of blurred vision occurred with placebo and one patient receiving rosuvastatin 20 mg had a vesicular rash during the OL phase. There was no hepatic, skeletal muscle or renal adverse events reported.
Stein et al.[33] (2017) HYDRA Rosuvastatin 20 mg vs placebo Patients	DB, MC, RCT, XO Patients 6 to <18 years of age with HoFH	N=14 12 weeks (followed by 12 weeks of OL rosuvastatin)	Primary: Change in LDL-C Secondary: Lipoproteins, apolipoproteins	Primary: Mean LDL-C was 481 mg/dL (range, 229 to 742 mg/dL) on placebo and 396 mg/dL (range, 130 to 700 mg/dL) on rosuvastatin, producing a mean 85.4 mg/dL (22.3%) difference (P=0.005). Efficacy was similar regardless of age or use of ezetimibe or apheresis, and was maintained for 12 weeks. Secondary: Reductions in apo B, and other apo B-containing lipoproteins, paralleled those for LDL-C, with mean absolute reductions of 33 mg/dL (17.1%) in apo B (P=0.024) and 93.2 mg/dL (22.9%) in non–HDL-C (P=0.003). Mean absolute reductions in triglycerides of 39.6 mg/dl (30.4%; P=0.004) were seen with rosuvastatin 20 mg compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
discontinued all lipid-lowering treatment except ezetimibe and/or apheresis.				
Braamskamp et al.[34] (2015) CHARON Rosuvastatin (5-mg starting dose was titrated at 3-monthly intervals to a maximum tolerated dose of 10 mg for 6 to 9 year olds or 20 mg for 10 to 17 year olds)	MC, OL Patients 6 to 17 years of age with HeFH and fasting LDL-C >190 mg/dL or >158 mg/dL with other cardiovascular risk factors	N=197 2 years	Primary: Percentage change from baseline in fasting LDL-C after 3, 12, and 24 months of treatment Secondary: Percentage change from baseline in HDL-C, TC, TG, non-HDL-C, ApoA-1 and ApoB; safety	Primary: At three months, the least-square mean percentage reductions in LDL-C were 41, 41, and 35%, in patients aged six to nine, 10 to 13, and 14 to 17 years, respectively (P<0.001 for all three age groups vs baseline). This effect was sustained over the two years of treatment; the mean percentage reductions in LDL-C at 24 months were 43, 45, and 35%, respectively. Secondary: At 24 months, there was a significant reduction in TC (P<0.001), non-HDL-C (P<.001), and ApoB (P<0.001) and a significant increase in HDL-C level (P≤0.001) compared with baseline across all age groups and overall. The most commonly reported adverse events were nasopharyngitis, headache, influenza, and vomiting (all ≥10% of total patients). Rosuvastatin treatment did not appear to impact height, weight, or sexual maturation.
Avis et al.[35] (2007) Standard statin therapy (pravastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, atorvastatin) vs placebo	MA (6 RCTs) Patients <18 years of age with heFH	N=798 Up to 2 years	Primary: Percentage change in TC, LDL-C, TG, HDL-C, apo B and apo AI; difference in absolute changes in IMT; safety Secondary: Not reported	Primary: Statin therapy was associated with a 23% reduction in TC compared to placebo (95% CI, 19 to 27; P value not reported). Statin therapy was associated with a 30% reduction in LDL-C compared to placebo (95% CI, 24 to 36; P value not reported). Statin therapy was associated with a 3.6% increase in HDL-C compared to placebo (95% CI, 1.33 to 5.94; P value not reported). Statin therapy was associated with a 25% reduction in apo B compared to placebo (95% CI, 19 to 31; P value not reported). Statin therapy was associated with a 2.4% reduction in apo AI compared to placebo (95% CI, 0.41 to 4.45; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Statin therapy was associated with a significant carotid IMT regression compared to placebo (P=0.02). Statin therapy was not associated with a significant risk of adverse events compared to placebo (RR, 0.99; 95% CI, 0.79 to 1.25). Statin therapy was not associated with a significant risk of AST (RR, 0.98; 95% CI, 0.23 to 4.26), ALT (RR, 2.03; 95% CI, 0.24 to 16.95) or CK elevation (RR, 1.38; 95% CI, 0.18 to 10.82) compared to placebo. Secondary: Not reported
Shafiq et al.[36] (2007) Statins (lovastatin, pravastatin, simvastatin, atorvastatin vs placebo	MA (6 trials) DB, RCTs comparing statins with placebo in pediatric and adolescent patients with FH	N=798 12 to 104 weeks	Primary Percent change in LDL-C, TC, TG, HDL-C Secondary: Not reported	Primary Statin therapy was associated with a significant reduction in LDL-C compared to placebo. Statin therapy was associated with a significant reduction in TC compared to placebo. Statin therapy was associated with a significant reduction in TG compared to placebo. Statin therapy was associated with a significant increase in HDL-C compared to placebo. Secondary: Not reported
Marais et al.[37] (2008) Rosuvastatin 80 mg QD for 6 weeks vs	DB, RCT, XO Patients >10 years of age, weighing ≥32 kg with hoFH, fasting LDL-C >500 mg/dL, TG <600 mg/dL and either xanthomata	N=44 30 weeks (includes the 18 week OL titration phase)	Primary Percent change in LDL-C from baseline to week 18 Secondary Response rate; percent change	Primary Rosuvastatin 20 to 80 mg achieved a significant reduction in LDL-C from baseline after 18 weeks of therapy (21.4%; P<0.0001). Patients without a portacaval shunt and those not receiving plasmapheresis who received rosuvastatin 20 to 80 mg experienced a 15% reduction in LDL-C from baseline after 18 weeks of therapy (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 80 mg QD for 6 weeks All patients were randomized following a 18 week OL titration phase during which patients received rosuvastatin 20 mg QD for 6 weeks, titrated up to 40 mg/day for 6 weeks, titrated up to 80 mg/day for another 6 weeks, all after a 4 week dietary lead in period.	before 10 years of age or both parents with FH		in TC, apo B, TG and HDL-C	Rosuvastatin was associated with an overall 72% response rate (≥15% reduction in baseline LDL-C) (P value not reported). Rosuvastatin 20 to 80 mg was associated with a significant reduction in TC and apo B from baseline after 18 weeks of therapy (20%; P<0.0001). Rosuvastatin 20 to 80 mg was associated with a nonsignificant increase in TG and HDL-C from baseline after 18 weeks of therapy (3.3 and 3.1%, respectively; P>0.05). At week 24, rosuvastatin and atorvastatin did not differ in the magnitude of LDL-C reduction from baseline (19.1 vs 18.0%; P=0.67). At week 24, there was no significant difference between treatments in reductions from baseline TC (17.6 vs 17.9%; P=0.91), TG (6.3 vs 13.9%; P=0.21) or apo B (11.4 vs 11.7%; P=0.90). The only significant difference between the two treatments was in the change from baseline in apo AI. While patients receiving rosuvastatin experienced an increase, atorvastatin-treated patients exhibited a reduction in apo AI (P=0.001).
Arca et al.[38] (2007) Atorvastatin 10 mg/day, titrated up to 80 mg/day vs fenofibrate 200 mg/day	OL, RCT Patients 30 to 75 years of age with diagnosis of familial combined hyperlipidemia with TC and/or TG levels ≥90th Italian population percentiles, and/or hyper-apobeta-lipoproteinemia	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A and endothelin-1 Secondary: Not reported	Primary: Atorvastatin was associated with a significant 9% reduction in TC compared to fenofibrate (95% CI, 3.0 to 15.1; P=0.004). Atorvastatin was associated with a significant 17% reduction in LDL-C compared to fenofibrate (95% CI, 8.0 to 26.1; P<0.001). Fenofibrate was associated with a significant 15.5% reduction in TG compared to atorvastatin (95% CI, 3.35 to 27.70; P=0.013). Fenofibrate was associated with a significant 14.2% increase in HDL-C compared to atorvastatin (95% CI, 3.8 to 24.6%; P=0.008). Fenofibrate was associated with a significant 5.2 and 22.0% increase in apo AI and apo AII compared to atorvastatin (P=0.044 and P<0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Fenofibrate was associated with a significant 16.7% reduction in endothelin-1 from baseline (P<0.05). Atorvastatin was not associated with a significant change in endothelin-1 (P value not reported). Secondary: Not reported
Gagné et al.[39] (2002) Statin 40 mg for up to 14 weeks, followed by the addition of ezetimibe 10 mg QD for another 12 weeks, administered as separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily and addition of ezetimibe 10 mg QD daily for another 12 weeks, administered as separate vs	DB, MC, RCT Patients ≥12 years old (or with body weight ≥40 kg) with hoFH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on atorvastatin or simvastatin 40 mg/day)	N=50 26 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (20.7 vs 6.7%; P=0.007). Secondary: TC was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (18.7 vs 5.3%; P<0.01). There was no statistically significant difference in any of the other secondary outcome measures between the two groups (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily Statins used in the study included simvastatin and atorvastatin.				
Hypercholesterolemia (Single Entity Agents)				
Koshiyama et al.[40] (2008) KISHIMEN Pitavastatin 1 to 2 mg/day	MC, OL, PRO Patients with TC ≥220 mg/dL and TG <400 mg/dL	N=178 12 months	Primary: Changes from baseline in LDL-C, HDL-C, remnant-like particle cholesterol, TG and hsCRP Secondary: Not reported	Primary: LDL-C was significantly reduced by 32.6, 31.0 and 30.3% after three, six and 12 months, respectively (P value not reported). HDL-C was significantly increased by 3.1, 5.9 and 2.6% after three, six and 12 months, respectively. In patients with baseline HDL-C <40 mg/dL, HDL-C increased by 16.2, 22.4 and 19.0% after three, six and 12 months (P values not reported). Remnant-like particle cholesterol were significantly reduced by 14.0, 20.2 and 22.8% after three, six and 12 months, respectively (P value not reported). TG was significantly reduced by 17.7 and 15.9% after three and 12 months, respectively, in patients whose baseline TG >150 mg/dL, although TG was not significantly reduced in the overall population (P value not reported). hsCRP were significantly reduced in 31 patients after 12 months (P<0.01). hsCRP was significantly reduced in patients with diabetes (P<0.05). Secondary: Not reported
Motomura et al.[41] (2009)	MC, OL, PRO Patients >20 years of age with type 2	N=65 6 months	Primary: Changes from baseline in lipid panel and	Primary: Significant reductions in TC, LDL-C and TG and significant increases in HDL-C were observed at one, three and six months after treatment with pitavastatin was initiated (P<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Pitavastatin 2 mg/day	diabetes, LDL-C ≥120 mg/dL, TG <400 mg/dL, HbA_{1c} <9.0% and not on hypolipidemic medication for the preceding 4 weeks		hsCRP Secondary: Not reported	After six months, average reductions in TC, LDL-C and TG were: 27.1, 41.1 and 6.2%. Average increase in HDL-C at six months was 4.5%. Changes in hsCRP were not significant after three months of treatment (0.49 to 0.43 mg/L; P=0.057), but was significantly reduced at six months (0.49 to 0.37 mg/L; P<0.05). Secondary: Not reported
Ose et al.[42] (2010) Pitavastatin 4 mg QD	ES, OL Patients with primary hypercholesterolemia or combined dyslipidemia who had previously received pitavastatin, atorvastatin or simvastatin for 12 weeks during a DB, Phase III trial	N=1,353 52 weeks	Primary: Safety and tolerability Secondary: Proportion of patients achieving NCEP and European Atherosclerosis Society LDL-C goals (not specified), changes from baseline in lipid profiles	Primary: Overall, 54.8% of patients reported experiencing at least one treatment emergent adverse event, 12.0% of which were determined by the investigators to be related to pitavastatin. Furthermore, 4.1% (n=55) of patients discontinued due to treatment emergent adverse events and 3.6% (n=49) of patients experienced a serious treatment emergent adverse event, none of which were related to pitavastatin. Two patients died during the trial, neither of which were determined to be related to pitavastatin. The most commonly reported adverse events were increased CK levels (5.8%), nasopharyngitis (5.4%) and myalgia/myalgia intercostals (4.1%). Secondary: At the end of the original DB phases, 71.5 and 69.4% of patients had achieved the LDL-C goals. After 52 weeks, 74.0 and 73.5% of patients achieved the goals. The reductions in mean LDL-C observed at the end of the DB phases were sustained throughout the ES. HDL-C showed a gradual increase; mean HDL-C at week 52 was 57.0 mg/dL (equivalent to a mean change of 14.3% above baseline and 8.7% above end of the DB phases; P value not reported). Non-HDL-C was associated with a sustained decrease from baseline during the ES (38.9% at end of DB phases and 39.6% at week 52). Concentrations of TG, TC, apo AI, apo B, TC:HDL-C, non-HDL-C:HDL-C and apo B:AI were similar at the end of the ES to those observed at the end of the DB phases.
Stein et al.[43] (2007)	MC, OL Patients ≥18 years	N=1,380 ≤96 weeks	Primary: Percentage of patients who	Primary: At 12 weeks, 83% of patients achieved an LDL-C goal (95% CI, 81 to 85; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Rosuvastatin 40 mg/day for ≤96 weeks All patients entered a 6 week dietary lead in period.	of age with LDL-C ≥190 to ≤260 mg/dL and TG <400 mg/dL		achieved NCEP ATP III LDL-C goals (<160, <130 or <100 mg/dL) at 12 weeks Secondary: Reduction in LDL-C, HDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B	Secondary: At 48 weeks, rosuvastatin was associated with a significant reduction from baseline in LDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B (P<0.0001). At 48 weeks, rosuvastatin was associated with a significant increase from baseline in HDL-C (11%; P<0.0001). During the 96-week trial period, 13.0% of patients experienced a serious adverse event, 0.4% of these patients died and 2.0% experienced myalgia (P value not reported).
Preston et al.[44] (2007) RESPOND Amlodipine 5 or 10 mg QD plus atorvastatin 10, 20, 40 or 80 mg QD (all possible dosing combinations) vs amlodipine 5 or 10 mg QD vs atorvastatin 10, 20, 40 or 80 mg	DB, RCT Patients 18 to 75 years of age with HTN and dyslipidemia	N=1,660 8 weeks	Primary: Mean change from baseline in SBP and LDL-C Secondary: Augmentation of BP lowering with the addition of atorvastatin and augmentation of LDL-C lowering with the addition of amlodipine, reduction in 10 year Framingham risk scores,	Primary: Regardless of dose, combination therapy was associated with significantly greater reductions in SBP compared to atorvastatin (P<0.001 for all comparisons). Overall, combination therapy and atorvastatin achieved comparable decreases in LDL-C. Only the combination of amlodipine 5 mg plus atorvastatin 10 mg achieved significant reductions in LDL-C compared to atorvastatin 10 mg (P=0.007). Secondary: Regardless of dose, there was no difference in terms of SBP lowering between combination therapy and amlodipine (P>0.05 for all comparisons). Regardless of dose, combination therapy significantly reduced LDL-C compared to amlodipine (P<0.001 for all comparisons). A maximal reduction in 10 year Framingham risk scores was observed with combination therapy (5/80 and 10/80 mg; P values not reported). The proportion of patients who discontinued therapy due to adverse effects was similar with all treatments (5.6 vs 5.4 vs 4.1, respectively; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
QD vs placebo			adverse effects	
Ballantyne et al.[45] (2003) Ezetimibe 10 mg QD and atorvastatin 10 to 80 mg QD vs ezetimibe 10 mg QD vs atorvastatin 10 to 80 mg QD vs placebo	DB, PC, RCT Men and women aged ≥18 years with primary hypercholesterolemia (LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL)	N=628 12 weeks	Primary: Percentage reduction in direct LDL-C from baseline to final assessment Secondary: Change from baseline to final assessment for calculated LDL-C, TC, TG, HDL-C, TC:HDL-C ratio, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, Lp(a), direct LDL-C:HDL-C ratio, adverse events	Primary: There was a significantly greater mean reduction of direct LDL-C from baseline to final assessment in the ezetimibe plus atorvastatin group compared to either atorvastatin alone (P<0.01) or ezetimibe alone (P<0.01). Mean changes in direct LDL-C ranged from -50 to -60% in the combination group compared to -35 to -51% in the atorvastatin alone group (P<0.01). Secondary: Calculated LDL-C was also significantly reduced more commonly in the combination group than all doses of atorvastatin monotherapy (P<0.01). Greater reductions in LDL-C, TC, and TG were observed with increasing doses of atorvastatin monotherapy. However, there was not a favorable dose response with HDL-C. There were similar reductions in LDL-C (50 vs 51%), TC:HDL-C ratio (43 vs 41%), and TG (both 31%) with coadministration of ezetimibe plus atorvastatin 10 mg and the maximal dose of atorvastatin monotherapy, respectively. However, there was a significantly greater increase in HDL-C (9 vs 3%) with the combination group. Reductions in apo B, non–HDL-C, and direct LDL-C:HDL-C ratio from baseline were significantly greater in the combination group compared to both atorvastatin monotherapy (P<0.01 for all) and ezetimibe monotherapy (P<0.01 for all). However, increases in HDL_2-C (P=0.53), HDL_3-C (P=0.06), apo AI (P=0.31), and Lp(a) (P=0.50) did not significantly differ between the combination therapy and atorvastatin monotherapy groups. There also was no significant difference between the combination therapy and ezetimibe monotherapy groups for increases in these same parameters: HDL_2-C (P=0.08), HDL_3-C (P=0.67), apo AI (P=0.80), and Lp(a) (P=0.92).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				The combination of ezetimibe plus atorvastatin was well-tolerated. Treatment-emergent adverse events were reported in 17% of patients receiving atorvastatin monotherapy and 23% of patients receiving combination therapy. The majority of adverse events were mild to moderate in severity.
Stein et al.[46] (2004) Ezetimibe 10 mg QD and atorvastatin 10 mg QD (titrated up to 40 mg/day) vs atorvastatin 20 mg QD (titrated up to 80 mg/day)	DB, DD, MC Patients ≥18 years of age with primary hypercholesterolemia and documented CHD, ≥2 cardiovascular risk factors, or heFH with an LDL-C level ≥130 mg/dL despite treatment with atorvastatin 10 mg	N=621 14 weeks	Primary: Percentage of patients achieving an LDL-C level ≤100 mg/dL after 14 weeks randomization Secondary: Effects on other lipid parameters four weeks after randomization	Primary: When compared to atorvastatin monotherapy, a significantly higher percentage of patients in the ezetimibe and atorvastatin reached an LDL-C level ≤100 mg/dL after 14 weeks randomization, respectively (7 vs 22%; P<0.01). Secondary: When compared to atorvastatin monotherapy, significant reductions in LDL-C, TC and TG levels were observed in patients in the ezetimibe and atorvastatin (P<0.01). Respectively, percent changes between combination vs atorvastatin monotherapy were -22.8 vs -8.6% (mean change) in LDL-C levels, -17.3 vs -6.1% in TC levels (mean change), and -9.3 vs -3.9% (median change) in TG levels (P<0.01 for all). Nonsignificant changes were observed in HDL-C levels.
Conard et al.[47] (2008) Ezetimibe 10 mg QD and atorvastatin 20 mg QD vs atorvastatin 40 mg QD	DB, MC, PG, RCT Patients 18 to 79 years of age at moderately high risk for CHD who were receiving atorvastatin 20 mg QD with LDL-C levels of 100 mg/dL to 160 mg/dL and TG ≤350 mg/dL	N=196 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <100 mg/dL, percent change TG, TC, HDL-C, non-HDL-C, apo AI, apo B, TC: HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C,	Primary: Treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-31 vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe plus atorvastatin achieved the NCEP ATP III LDL-C goal <100 mg/dL compared to atorvastatin 40 mg (84 vs 49%, P<0.001). Treatment with ezetimibe plus atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C than treatment with atorvastatin 40 mg (P<0.001). There was no significant difference in HDL-C, TG, apo AI, and hsCRP among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			hsCRP	
Leiter et al.[48] (2008) Ezetimibe 10 mg QD and atorvastatin 40 mg QD vs atorvastatin 80 mg QD	DB, MC, PG, RCT Patients 18 to 79 years of age at high risk for CHD (CHD or those with a CHD risk equivalent medical condition) who were receiving atorvastatin 40 mg QD with LDL-C levels of 70 mg/dL to 160 mg/dL and TG ≤350 mg/dL	N=579 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <70 mg/dL, percent change TG, TC, HDL-C, non-HDL-C, apo AI, apo B, TC: HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C, hsCRP	Primary: Treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-27 vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe plus atorvastatin achieved the NCEP ATP III LDL-C goal <70 mg/dL compared to atorvastatin 80 mg (74 vs 32%, respectively; P<0.001). Treatment with ezetimibe plus atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C compared to atorvastatin 80 mg (P<0.001). There was no significant difference in HDL-C, TG, apo AI, and hsCRP among the treatment groups.
Zieve et al.[49] (2010) ZETELD Ezetimibe 10 mg QD for 12 weeks and atorvastatin 10 mg QD for 6 weeks, followed by atorvastatin 20 mg QD for 6 weeks vs atorvastatin 20 mg QD for 6	DB, MC, PG, RCT Patients ≥65 years of age at high risk for CHD with or without atherosclerotic vascular disease who had not reached a LDL-C <70 mg/dL or <100 mg/dL, respectively, after receiving atorvastatin 10 mg/day	N=1,053 12 weeks	Primary: Percent change in LDL-C after six weeks Secondary: Percentage of patients achieving LDL-C <70 mg/dL and <100 mg/dL for high-risk patients without AVD and <70 mg/dL for high-risk patients with	Primary: After six weeks of therapy, treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to atorvastatin monotherapy (-29 vs -15%; P<0.001). Secondary: The percentage of patients achieving LDL-C <70 mg/dL and LDL-C <100 mg/dL (without AVD) or <70 mg/dL (with AVD) was significantly greater with ezetimibe plus atorvastatin compared to atorvastatin monotherapy at week six and week 12 (P<0.001). After six weeks of therapy, treatment with ezetimibe plus atorvastatin led to significantly greater changes in HDL-C (+3 vs +1%; P=0.02), TC (-16 vs -8%; P<0.001), non-HDL-C (-24 vs -11%; P<0.001), TG (-13 vs -6%; P<0.001), apo B (-17 vs -8%; P<0.001), TC:HDL-C (-17 vs -8%; P<0.001), LDL-C:HDL-C (-27 vs -13%; P<0.001), apo B:apo AI (-15 vs -5%; P<0.001), and non- HDL-C:HDL-C (-24 vs -11%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
weeks, followed by atorvastatin 40 mg for 6 weeks			AVD, HDL-C, non-HDL-C, TG, TG, apo B, apo AI, TC:HDL-C, apo B:apo AI, LDL-C:HDL-C, non-HDL-C:HDL-C	At week 12, significantly greater changes in favor of ezetimibe plus atorvastatin occurred in HDL-C, TC, non-HDL-C, apo B, apo AI, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C. There was no significant difference among the treatment groups in apo AI at week six, high-sensitivity C-reactive protein at weeks six and 12, and TG at week 12.
Piorkowski et al.[50] (2007) Atorvastatin 40 mg QD vs atorvastatin 10 mg QD and ezetimibe 10 mg QD	RCT Patients 18 to 80 years of age with clinically stable angiographically documented CHD and LDL-C >2.5 mmol/L despite ongoing atorvastatin 10 to 20 mg/day, receiving aspirin and clopidogrel	N=56 4 weeks	Primary: Change in liver transaminases, CK, HDL-C, LDL-C, and TG from baseline, percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL-C in either group. Both groups exhibited a statistically significant reduction in LDL-C from baseline (P<0.005). There was no statistically significant difference between the two groups in degree of LDL-C reduction from baseline. Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in TG level from baseline (P<0.005 and P<0.05, respectively). There was no statistically significant difference between the two groups in the percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L). Secondary: Not reported
Goldberg et al.[51] (2006) VYTAL Atorvastatin 10, 20, or 40 mg/day vs	DB, MC, PG, RCT Adult patients with type 2 diabetes between 18 and 80 years of age with HbA_{1c} ≤8.5%, LDL-C >100	N=1,229 6 weeks	Primary: Percent reduction in LDL-C level at week six Secondary: Proportion of	Primary: Patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week six of the study compared to patients receiving atorvastatin 10 or 20 mg (53.6, 38.3, and 44.6%, respectively; P<0.001). Patients randomized to simvastatin 40 mg plus ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week six of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 20 or 40 mg/day and ezetimibe 10 mg/day daily	mg/dL and a TG level <400 mg/dL		patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of patients who achieved LDL-C level of <100 mg/dL, percent change from baseline in HDL-C, non-HDL-C, TC, TG, and CRP	the study compared to patients receiving atorvastatin 40 mg (57.6 and 50.9%, respectively; P<0.001). Secondary: A greater proportion of patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy achieved LDL-C <70 mg/dL compared to patients receiving atorvastatin 10 or 20 mg (59.7, 21.5, and 35%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 40 mg plus ezetimibe 10 mg therapy achieved LDL-C <70 mg/dL compared to patients receiving atorvastatin 40 mg (74.4 and 55.2%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 20 mg plus ezetimibe 10 mg therapy achieved LDL-C <100 mg/dL compared to patients receiving atorvastatin 10 or 20 mg (90.3, 70, and 82.1%, respectively; P=0.007). A greater proportion of patients randomized to simvastatin 40 mg plus ezetimibe 10 mg therapy achieved LDL-C <100 mg/dL compared to patients receiving atorvastatin 40 mg (93.4 and 88.8%, respectively; P=0.07). Patients randomized to simvastatin plus ezetimibe combination therapy, at all doses, experienced a significant increase in HDL-C level (P≤0.001), a greater reduction in TC, and non-HDL-C (P<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy experienced a significant reduction in CRP and TG level compared to patients receiving atorvastatin (P=0.02). Side effects were similar in the simvastatin plus ezetimibe and atorvastatin groups (19.85 vs 22.7%).
Winkler et al.[52] (2007) Fluvastatin 20	MA (30 trials) DB, PC, RCTs assessing ≥6 weeks	N=7,043 ≥6 weeks	Primary: Major adverse cardiovascular events defined	Primary: Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of any major adverse cardiovascular events compared to placebo (16 vs 22%; HR, 0.728; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg, 40 mg, and 80 mg (pooled group) vs placebo	of fluvastatin therapy in dyslipidemic patients with and without metabolic syndrome		as cardiovascular disease-related death, nonfatal MI, and cardiac re-vascularization, LDL-C, HDL-C, TC, TG, non-HDL-C, apo B Secondary: Not reported	0.6 to 0.9; P=0.001). The difference in the incidence of major adverse cardiovascular events between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.083). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death compared to placebo (3 vs 4.9%; HR, 0.62; 95% CI, 0.4 to 0.95; P=0.03). The difference in the incidence of cardiovascular death between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.478). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular intervention compared to placebo (12 vs 16%; HR, 0.75; 95% CI, 0.59 to 0.93; P=0.011). The difference in the incidence of cardiovascular intervention between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.125). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death or nonfatal MI compared to placebo (6.6 vs 9.9%; HR, 0.65; 95% CI, 0.48 to 0.87; P=0.005). The difference in the incidence of cardiovascular death or nonfatal MI between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.288). There was no statistically significant difference in the incidence of nonfatal MI, all-cause mortality, or non-cardiovascular-related death between pooled fluvastatin- and placebo-treated patients whether or not they had the metabolic syndrome (P>0.05). In all patients, pooled fluvastatin was associated with a significant reduction from baseline in LDL-C, TC, TG, non-HDL-C, and apo B compared to placebo (P<0.001). Patients with and without the metabolic syndrome taking fluvastatin experienced similar benefits in terms of LDL-C, TC, non-HDL-C, and apo B reduction from baseline.

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				Patients with the metabolic syndrome experienced a greater increase in HDL-C and a greater reduction in TG from baseline compared to patients without the metabolic syndrome (P<0.01). Secondary: Not reported
Stein et al.[53] (2008) Fluvastatin XL 80 mg QD vs ezetimibe 10 mg QD vs fluvastatin XL 80 mg QD and ezetimibe 10 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with dyslipidemia who had previously documented muscle related side effects that had led to cessation of statin treatment or patients currently receiving statin treatment whose quality of life was affected by muscle related side effects and required switching to an alternative treatment	N=218 12 weeks	Primary: Percent decrease in LDL-C Secondary: LDL:HDL-C, TC, TG, apo B, proportion of patients achieving LDL-C goal	Primary: LDL-C was reduced by 15.6, 32.8, and 46.1% with ezetimibe monotherapy, fluvastatin XL monotherapy, and fluvastatin XL plus ezetimibe combination therapy, respectively (fluvastatin XL vs ezetimibe: -17.1%; P<0.0001; fluvastatin XL plus ezetimibe vs ezetimibe: -30.4%; P<0.0001). Secondary: Treatment with fluvastatin XL monotherapy and fluvastatin XL plus ezetimibe combination therapy led to a greater reduction in LDL:HDL-C, TC, TG, and apo B levels compared to ezetimibe monotherapy (all, P<0.0001). More patients achieved their target LDL-C goal with fluvastatin XL monotherapy and fluvastatin XL plus ezetimibe combination therapy compared to ezetimibe monotherapy (P<0.001 for fluvastatin XL monotherapy or combination therapy vs ezetimibe monotherapy). There were no serious adverse events, rhabdomyolysis, or creatine kinase increases ≥10 times upper limit of normal. Muscle related side effects were reported in 24% of patients receiving ezetimibe monotherapy compared to 17% of patients in the fluvastatin XL group and 14% of patients in the fluvastatin XL plus ezetimibe combination group. Differences in recurrence of muscle related side effects were not statistically different between treatment groups.
Alvarez-Sala et al.[54] (2008) Fluvastatin XL 80 mg QD (nighttime) and	MC, OL, PG, RCT Patients 18 to 75 years of age with primary hypercholesterolemia (LDL-C ≥130	N=89 12 weeks	Primary: Percentage change in LDL-C Secondary: Percentage	Primary: Fluvastatin XL plus ezetimibe lowered mean LDL-C from 197 mg/dL to 97 mg/dL (-49.9%) and fluvastatin XL alone lowered mean LDL-C from 216 to 135 mg/dL (-35.2%) after 12 weeks of therapy (P<0.001). Secondary: Fluvastatin XL plus ezetimibe combination was associated with a significantly

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ezetimibe 10 mg QD vs fluvastatin XL 80 mg QD (nighttime)	mg/dL and TG ≤400 mg/dL)		change in HDL-C and TG, proportions of patients achieving NCEP ATP III LDL-C goals, change in hsCRP and other markers of inflammation, and safety	greater reduction from baseline in TC, TG, and apo B than fluvastatin XL alone (P<0.05 for all). There was no significant change in HDL-C level with either treatment regimen. A greater proportion of patients receiving the fluvastatin XL plus ezetimibe achieved NCEP ATP III LDL-C goals at week 12 compared to those receiving fluvastatin XL alone (86.5 vs 66.7%; P=0.042). There were no significant changes in levels of hsCRP with either treatment regimen. In patients with higher baseline hsCRP levels, the coadministration of fluvastatin XL with ezetimibe was associated with a reduced level of this inflammatory marker. Treatment with fluvastatin XL plus ezetimibe or fluvastatin XL alone was associated with significant reductions in IL-1β (21%; P<0.001 and 13%; P<0.002, respectively). No significant changes were seen in levels of interleukin-6, tumor necrosis factor-α, soluble P-selectin, or soluble vascular cell adhesion molecule-1. There was no significant difference in the incidence of adverse events between the treatment groups. Most adverse events were mild or moderate in intensity, with headache being the most common (8.5%).
Messerli et al.[55] (2006) AVALON Amlodipine 5 mg/day for 8 weeks, followed by the addition of atorvastatin 10 mg/day for another 8 weeks vs atorvastatin 10	DD, MC, OL, RCT Patients with HTN and dyslipidemia	N=847 28 weeks	Primary: Proportion of patients who reached the JNC 7 and NCEP ATP III goals, side effects Secondary: Not reported	Primary: A significantly greater proportion of patients receiving combination therapy achieved JNC 7 and NCEP ATP goals at eight weeks compared to patients receiving amlodipine or patients receiving atorvastatin monotherapy (45.0 vs 8.3 and 28.6%, respectively; P<0.001). The incidence of side effects was similar across all treatments (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day for 8 weeks, followed by the addition of amlodipine 5 mg/day for an additional 8 weeks vs amlodipine-atorvastatin 5-10 mg/day for 16 weeks vs placebo for 16 weeks All patients received an additional 12 weeks of OL treatment following the first 16 weeks of therapy.				
Hunninghake et al.[56] (2001) Colesevelam 3.8 g/day vs	DB, MC, PC, RCT Patients with LDL-C ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in TC, HDL-C, TG,	Primary: All treatments resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions from baseline were -12% with colesevelam (P<0.05), -38% with atorvastatin 10 mg (P<0.0001), -48% with colesevelam plus atorvastatin (P<0.0001) and -53% with atorvastatin 80 mg (P<0.0001), respectively. Secondary: Colesevelam reduced TC by six percent (P<0.05), increased HDL-C by three

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 10 mg/day vs colesevelam 3.8 g/day plus atorvastatin 10 mg/day vs atorvastatin 80 mg/day vs placebo			apo B, apo AI and Lp(a)	percent (P<0.05) and increased TG by 10% (P value not reported). Atorvastatin 10 mg reduced TC by 27% (P<0.0001), increased HDL-C by eight percent (P<0.05) and reduced TG by 24% (P<0.05). Colesevelam plus atorvastatin reduced TC by 31% (P<0.0001), increased HDL-C by 11% (P<0.05) and reduced TG by one percent (P value not reported). Atorvastatin 80 mg reduced TC by 39% (P<0.0001), increased HDL-C by five percent (P<0.05) and reduced TG by 33% (P<0.0001). Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam plus atorvastatin. No significant differences in HDL-C were found between the treatment groups (P values not reported). Apo B levels decreased significantly for with all treatments relative to baseline (P<0.01). No significant changes in apo AI and Lp(a) were reported (P values not reported).
Brown et al.[57] (1990) Colestipol 5 to 10 g TID plus niacin 125 mg BID titrated to 1 to 1.5 g TID vs Colestipol 5 to 10 g TID plus lovastatin 20 mg BID titrated to 40 mg BID vs	DB, RCT Men ≤62 years of age with elevated apo B and a family history of CAD	N=120 32 months	Primary: Average change in the percent stenosis for the worst lesion in each of the nine proximal segments Secondary: Average changes in all lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or	Primary: On average, placebo (conventional therapy) increased the index of stenosis by 2.1 percentage points a baseline of 34%. By contrast, it decreased by 0.7 percentage points with colestipol plus lovastatin and by 0.9 percentage points with colestipol and niacin (P<0.003 for trend). At trial end, on average, these nine lesions were almost 3 percentage points less severe among patients treated intensively compared to conventionally. This difference represents almost 1/10 of the amount of disease present at baseline (34% stenosis). Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease when looking at the effect of treatment on certain subsets of lesions (all lesions measured in each patient, lesions causing severe or mild stenosis and those that did not cause total occlusion at baseline). The results with both treatment groups were significantly difference from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo (or colestipol if LDL-C was elevated)			<50% (mild) stenosis at baseline	
Kerzner et al.[58] (2003) Ezetimibe 10 mg/day vs lovastatin 10, 20 or 40 mg/day vs ezetimibe 10 mg/day plus lovastatin 10, 20 or 40 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with mean plasma LDL-C 145 to 250 mg/dL as calculated by Friedewald equation and mean TG ≤350 mg/dL	N=548 12 weeks	Primary: Percentage decrease from baseline in LDL-C Secondary: Changes from baseline in calculated LDL-C, TC, TG, HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, apo AI and LDL-C:HDL-C; adverse events	Primary: The reduction in LDL-C was significantly greater with combination therapy compared to either lovastatin or ezetimibe (P<0.01 for both). The mean percentage decrease in LDL-C with combination therapy was significantly greater than the decrease obtained from the corresponding lovastatin dose or next higher dose of lovastatin (P<0.01). The mean percentage change in LDL-C achieved with combination therapy (lovastatin 10 mg) was similar to lovastatin 40 mg (P=0.10). Secondary: In comparison to lovastatin, combination therapy significantly improved calculated LDL-C, TC, TG, HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, LDL-C:HDL-C (P<0.01 for all) and apo AI (P=0.04). Combination therapy significantly increased HDL-C with lovastatin doses of 20 and 40 mg compared to the same lovastatin dose administered as monotherapy (P<0.01 and P<0.02, respectively), and significantly decreased TG levels (P<0.01 for both). Treatment-related adverse events were reported by 16% of patients receiving lovastatin and 17% of patients receiving combination therapy. The safety profile for combination therapy was similar to that for lovastatin and placebo (P values not reported).
Lewis et al.[59] (2007) Pravastatin 80 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with hypercholesterolemia, LDL-C ≥100 and TG <400 mg/dL, with ≥6 month history of	N=326 36 weeks	Primary: Percent change from baseline at week 12 in LDL-C, TC and TG; ALT event rate (ALT at least two times the upper limit	Primary: Pravastatin was associated with a significant reduction in LDL-C, TC and TG at week 12 compared to placebo (P<0.0001). There was no significant difference between the two treatments in the ALT event rate at any time during the trial (P>0.05). By week 36, 7.5 and 12.5% of patients receiving pravastatin and placebo had at least one ALT event (P=0.1379).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	compensated liver disease		of normal for those with normal ALT at baseline or a doubling of the baseline ALT for those with elevated ALT at baseline) Secondary: Not reported	Secondary: Not reported
Melani et al.[60] (2003) Ezetimibe 10 mg/day vs pravastatin 10, 20 or 40 mg/day vs ezetimibe 10 mg/day plus pravastatin 10, 20 or 40 mg/day vs placebo	DB, MC, PC, RCT Patients 20 to 86 years of age with primary hypercholesterolemia (LDL-C 3.8 to 6.5 mmol/L as calculated by the Friedewald equation and TG ≤4.0 mmol/L)	N=538 12 weeks	Primary: Percent change from baseline LDL-C Secondary: Mean and percent changes from baseline in calculated LDL-C, TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo AI, apo B, HDL_2-C, HDL_3-C and Lp(a)	Primary: A mean percent change of -38 and -24% in LDL-C with combination therapy and pravastatin were observed (P<0.01). Combination therapy achieved a mean percentage change in LDL-C ranging from -34 to -41% compared to -20 to -29% with pravastatin (all doses). When combination therapy was compared to its corresponding pravastatin dose, the incremental mean percentage reductions in LDL-C were significant in favor of combination therapy (P≤0.01). In addition, combination therapy (pravastatin 10 mg) produced a larger mean percentage reduction in LDL-C compared to pravastatin 40 mg (P≤0.05). Secondary: In comparison to pravastatin, combination therapy improved calculated LDL-C, TG, TC, apo B, non-HDL-C, LDL-C:HDL-C and TC:HDL-C (P<0.01 for all). Both direct and calculated LDL-C levels at all pravastatin doses were significantly reduced with combination therapy (P<0.01). TG was also significantly reduced with combination therapy (pravastatin 10 and 20 mg) compared to pravastatin (P<0.05). Although combination therapy (pravastatin 10 and 40 mg) produced greater increases in HDL-C, it was not significant (P values not reported). The differences in change in HDL_2-C, HDL_3-C, apo AI and Lp(a) between combination therapy and pravastatin were not significant (P values not significant).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Combination therapy was well tolerated and the overall safety profile was similar to pravastatin and placebo. There was no evidence to suggest that combination therapy would increase the risk of developing any nonlaboratory adverse event (P value not reported).
Coll et al.[61] (2006) Ezetimibe 10 mg/day vs fluvastatin XR 80 mg/day	RCT Patients ≥18 years of age with HIV receiving stable HAART for ≥6 months and fasting LDL-C ≥3.30 mmol/L	N=20 6 weeks	Primary: LDL-C, TC, endothelial function Secondary: Not reported	Primary: Ezetimibe produced a 20% (P=0.002) LDL-C reduction and a 10% TC reduction (P=0.003). Fluvastatin XR produced a 24% (P=0.02) LDL-C reduction and a 17% TC reduction (P=0.06). There were no significant differences in lipid lowering ability between the two treatments (P values not reported). Ezetimibe did not produce significant changes in endothelial function, while fluvastatin XR produced an increase in the rate of endothelial function by 11% (P=0.5). Secondary: Not reported
Illingworth et al.[62] (1994) Lovastatin 10 to 80 mg/day vs niacin IR 0.25 mg to 1.5 g TID	MC, OL, RCT Patients 21 to 75 years of age with primary hypercholesterolemia and either an LDL-C >160 mg/dL and CHD or ≥2 CHD risk factors without CHD or LDL-C >190 mg/dL without CHD or ≥2 risk factors after rigorous diet	N=136 26 weeks	Primary: Change from baseline in lipid parameters Secondary: Safety	Primary: Lovastatin reduced TC, LDL-C and apo B significantly more than niacin (P<0.01 for all). At weeks 10, 18 and 26, LDL-C was reduced by 26, 28 and 32% with lovastatin compared to five, 16 and 21% with niacin, respectively. The target treatment goal of LDL-C <130 mg/day for patients with CHD or less than two risk factors was achieved in 14, 19 and 35% of patients receiving lovastatin compared to zero, 18 and 26% of patients receiving placebo at weeks 10, 18 and 26, respectively (P values not significant). For the majority of those patients with CHD or two or more risk factors in whom the LDL-C goal was <110 mg/dL, neither drug was effective in achieving this goal. In these patients only 13 and 11% achieved this goal at week 26, respectively (P value not reported). Niacin was more effective in decreasing TG at week 26 (P<0.01 vs lovastatin). Both treatments were effective in reducing VLDL-C, with no significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				difference observed between the two treatments (P value not reported). Niacin produced reductions in Lp(a) of 14, 30 and 35% at weeks 10, 18 and 26, whereas lovastatin had no effect (P<0.05 or P<0.01 between drugs at each time point). Niacin was significantly more effective at increasing HDL-C and apo AI (P<0.01 vs lovastatin), except for the change in apo A1 at week 10 (P value not reported). Niacin increased HDL-C by 20, 29 and 33% and apo AI by 11, 19 and 22% at weeks 10, 18 and 26. Lovastatin resulted in a modest increase in HDL-C and apo AI of 7 and 6%, respectively, at week 26. Secondary: Four deaths occurred in the trial, one with niacin and three with lovastatin. All were related to atherosclerosis, and none were deemed to be drug-related. Five and nine patients receiving lovastatin and niacin discontinued treatment because of adverse experiences (excluding deaths). For those who discontinued treatment, the reason was considered drug-related in four and eight patients receiving lovastatin and niacin (P value not significant). The major reasons for discontinuation of niacin were cutaneous complaints, including flushing, pruritis and rash. One patient discontinued lovastatin because of myalgias. Overall, patient tolerance to the treatments was better with lovastatin. Adverse events (in decreasing frequency) that occurred more frequently with niacin include flushing, paresthesia, pruritis, dry skin, nausea/vomiting, asthenia and diarrhea.
Eriksson et al.[63] (1998) Cholestyramine 16 g/day vs cholestyramine 8	MC, RCT Patients 30 to 65 years of age	N=2,036 12 months	Primary: Percent change from baseline in LDL-C Secondary: Compliance	Primary: Percent changes in LDL-C from baseline to endpoint with cholestyramine, cholestyramine plus pravastatin, pravastatin 20 mg and pravastatin 40 mg were -26 (95% CI, -23 to -29), -36 (95% CI, -33 to -39), -27 (95% CI, -25 to -29) and -32% (95% CI, -30 to -34). Secondary: Compliance rates with cholestyramine, cholestyramine plus pravastatin, pravastatin 20 mg and pravastatin 40 mg were 44, 53, 76 and 78% (P values

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
g/day plus pravastatin 20 mg/day vs pravastatin 20 or 40 mg/day				not reported). Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common with cholestyramine and cholestyramine plus pravastatin.
Hing Ling et al.[64] (2012) Atorvastatin 40 mg/day vs ezetimibe 10 mg/day plus simvastatin 40 mg/day All patients received atorvastatin 20 mg/day for six weeks at baseline.	AC, DB, MC, RCT Patients 18 to 79 years of age at high risk for CHD with primary hypercholesterolemia, LDL >100 mg/dL and <160 mg/dL, triglycerides <350 mg/dL, liver function tests within normal limits without active liver disease	N=250 6 weeks	Primary: Change from baseline in LDL-C, Secondary: TC, HDL, CRP, Apo AI, Apo B, TG, non-HDL, LDL-C/HDL ratio, TC/HDL ratio, non-HDL/HDL ratio, Apo AI/Apo B ratio	Primary: After six weeks, treatment with ezetimibe/simvastatin resulted in significantly greater reductions from baseline in LDL-C levels compared to treatment with atorvastatin 40 mg (-26.8 vs -11.8%; P<0.001). Secondary: Treatment with ezetimibe/simvastatin resulted in significantly greater reductions in TC (P<0.001), non-HDL-C (P<0.001), Apo B (P=0.002), Apo AI (P<0.001), and all lipid ratios (P<0.001 for all). There were no significant differences between treatments with regard to the change from baseline in TG (P=0.593), HDL-C (P=0.211), or CRP (P=0.785).
Pearson et al.[65] (2007) Atorvastatin 10, 20, 40 or 80 mg/day vs	MA (1 AC, DB; 3 PRO) Patients with primary hypercholesterolemia	N=4,373 12 weeks	Primary: Change from baseline in LDL-C level and hsCRP, proportion of patients reaching LDL-C target (<100	Primary: Across all doses, combination therapy was associated with significant reductions in LDL-C compared to simvastatin (52.5 vs 38.0%; P<0.001) and atorvastatin (53.4 vs 45.3%; P<0.001). Across all doses, combination therapy was associated with significant reductions in hsCRP compared to simvastatin (31.0 vs 14.3%; P<0.001). No significant difference was observed between combination therapy and atorvastatin (25.1 vs 24.8%; P value not reported). The reduction in hsCRP

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simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs placebo			or <70 mg/dL) Secondary: Not reported	was not significantly different between simvastatin 10 mg and placebo (P>0.10). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL compared to simvastatin (78.9 vs 43.1%; P<0.001) and atorvastatin (79.8 vs 61.9%; P<0.001). Similar results were observed with an LDL-C goal <70 mg/dL (37.0 vs 5.7%; P<0.001 and 36.2 vs 16.8%; P<0.001). Secondary: Not reported
Winkler et al.[66] (2009) Fluvastatin 80 mg/day plus fenofibrate 200 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 mg/day	MC, OL, RCT, XO Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist circumference ≥94 (men) or ≥80 cm (females) plus 1 of the following: TG ≥150 mg/dL, BP (≥85/≥130 mm Hg), fasting glucose ≥100 mg/dL or prevalent type 2 diabetes	N=75 6 weeks	Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions Secondary: Not reported	Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only reached significance in patients without small, dense LDL (P=0.043, P=0.006 and P=0.20). Reductions in TG were only significant with fluvastatin plus fenofibrate compared to ezetimibe plus simvastatin in patients with small, dense LDL (P=0.029). Increases in HDL-C and apo AI were only significant with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate in patients without small, dense LDL (P=0.020 and P=0.015). In patients with small, dense LDL, apo AII was markedly increased by fluvastatin plus fenofibrate, whereas ezetimibe plus simvastatin had no or little effect. Although only significant in small, dense LDL patients, apo CIII was more effectively reduce by fluvastatin plus fenofibrate, while the reduction of apo CII was more pronounced with ezetimibe plus simvastatin in all patients. Secondary: Not reported

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Becker et al.[67] (2008) Simvastatin 40 mg/day plus traditional counseling vs alternative treatment (therapeutic lifestyle changes and ingestion of red yeast rice and fish oil supplements)	RCT Patients 18 to 80 years of age with hypercholesterolemia who met NCEP ATP III criteria for primary prevention using statin therapy	N=74 3 months	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in HDL-C and TG, weight loss	Primary: There was a significant reduction in LDL-C with both simvastatin (39.6±20.0%) and alternative treatment (42.4±15.0%) (P<0.001), with no significant difference noted between the two treatments (P value not reported). Secondary: Alternative treatment was associated with a significant reduction in TG compared to simvastatin (29 vs 9%; 95% CI, 61.0 to 11.7; P=0.003). No differences between the two treatments were noted in improvements with HDL-C (P=0.21). Alternative treatment was associated with a significant reduction in weight loss compared to simvastatin (5.5 vs 0.4%; 95% CI, 5.5 to 3.4; P<0.001).
Meredith et al.[68] (2007) Simvastatin 20 mg QD vs simvastatin 80 mg QD vs placebo	DB, PG, RCT Patients who had undergone elective coronary angiography, had stable CAD and hsCRP >3 mg/L	N=107 16 weeks	Primary: Change from baseline in hsCRP Secondary: Change from baseline in LDL-C, TC and TG	Primary: There was no difference between simvastatin 20 and 80 mg in terms of change from baseline in hsCRP (P=0.82). Secondary: Simvastatin, regardless of dose, was more effective than placebo in baseline reductions of LDL-C (P<0.001). Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in hsCRP (P=0.007). Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in TC (P<0.001). Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in TG (P=0.01).
Knapp et al.[67] (2001)	DB, MC, PC, RCT Patients ≥18 years	N=258 6 weeks	Primary: Change from baseline in	Primary: LDL-C changes from baseline were -7 mg/dL with placebo (P<0.05), -31 mg/dL with colesevelam 3.8 g (P<0.0001), -48 mg/dL with simvastatin 10 mg

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Colesevelam 3.8 g/day vs simvastatin 10 mg/day vs colesevelam 3.8 g/day plus simvastatin 10 mg/day vs colesevelam 2.3 g/day vs simvastatin 20 mg/day vs colesevelam 2.3 g/day plus simvastatin 20 mg/day vs placebo	of age with LDL-C ≥160 mg/dL and TG ≤300 mg/dL who are not taking cholesterol lowering medication		LDL-C Secondary: Percent change in LDL-C; mean and percent change from baseline in TC, HDL-C, TG, apo B and apo AI	(P<0.0001), -80 mg/dL with colesevelam 3.8 g plus simvastatin 10 mg (P<0.0001), -17 mg/dL with colesevelam 2.3 g (P<0.0001), -61 mg/dL with simvastatin 20 mg (P<0.0001) and -80 mg/dL with colesevelam 2.3 g plus simvastatin 20 mg (P<0.0001), respectively. Secondary: LDL-C percent changes from baseline were -4% with placebo (P<0.05), -16% with colesevelam 3.8 g (P<0.0001), -26% with simvastatin 10 mg (P<0.0001), -42% with colesevelam 3.8 g plus simvastatin 10 mg (P<0.0001), -8% with colesevelam 2.3 g (P<0.0001), -34% with simvastatin 20 mg (P<0.0001) and -42% with colesevelam 2.3 g plus simvastatin 20 mg (P<0.0001), respectively. Significant changes from baseline were observed for all treatments in mean and percent change in TC (P<0.0001 for all, except colesevelam 2.3 g; P<0.05). Significant changes from baseline were observed for mean and percent change in HDL-C with simvastatin 10 mg (P<0.05), colesevelam 3.8 g plus simvastatin 10 mg (P<0.0001), colesevelam 2.3 g (P<0.05), simvastatin 20 mg (P<0.05) and colesevelam 2.3 g plus simvastatin 20 mg (P<0.05). Significant changes from baseline were observed for mean and percent change in TG with colesevelam 3.8 g (P<0.05), simvastatin 10 mg (P<0.05), simvastatin 20 mg (P<0.05) and colesevelam 2.3 g plus simvastatin 20 mg (P<0.05). Significant reductions from baseline for apo B were observed with all treatments. Reductions were significant (P<0.05) compared to placebo for all treatments except colesevelam 2.3 g (P value not reported). Significant increases in apo AI were achieved with all treatments except simvastatin 10 mg (P<0.05).
Chenot et al.[70] (2007)	RCT	N=60	Primary: Change from	Primary: Combination therapy produced a significant LDL-C reduction from baseline

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Simvastatin 40 mg/day vs simvastatin 40 mg/day plus ezetimibe 10 mg/day vs no lipid lowering therapy	Patients admitted for an acute MI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission	7 days	baseline to days two, four and seven in LDL-C; proportion of patients achieving an LDL-C <70 mg/dL Secondary: Not reported	on days two, four and seven (27, 41 and 51%, respectively; P<0.001). Simvastatin produced a significant LDL-C reduction from baseline on days two, four and seven (15, 27 and 25%, respectively; P<0.001). There was no significant reduction in LDL-C with no lipid lowering therapy (P≥0.09). Combination therapy achieved significant LDL-C reductions compared to simvastatin at days four (P=0.03) and seven (P=0.002). A greater proportion of patients receiving combination therapy achieved an LDL-C <70 mg/dL, compared to those receiving simvastatin at days four (45 vs 5%) and seven (55 vs 10%, respectively) (P values not reported). Secondary: Not reported
Davidson et al.[71] (2002) Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day	DB, MC, RCT Patients >18 years of age with primary hypercholesterolemia	N=668 20 week	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (49.9 vs 36.1%; P<0.001). Similar results were observed with combination therapy compared to ezetimibe (49.9 vs 18.1%; P<0.001). Combination therapy (simvastatin 10 mg) and simvastatin 80 mg produced a 44% reduction in LDL-C at 12 weeks (P value not reported). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks, compared to the next highest dose of simvastatin (P<0.01). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C and apo B at 12 weeks compared to simvastatin (P<0.01 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo				Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to simvastatin (P=0.03). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non–HDL-C and apo B at 12 weeks compared to ezetimibe (P<0.01 for all). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to ezetimibe (P=0.02). A significantly greater proportion of patients receiving combination therapy experienced a reduction in LDL-C >50% from baseline compared to simvastatin (P value not reported). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups (72 vs 69%, respectively; P value not reported).
Goldberg et al.[72] (2004) Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs	DB, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, ALT and AST ≤2 times the upper limit of normal, no active liver disease, CK ≤1.5 times the upper limit of normal	N=887 20 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP; proportion of patients reaching their NCEP ATP III	Primary: Averaged across all doses, combination therapy was associated with a significant 14.8% reduction in LDL-C at 12 weeks compared to simvastatin (53.2 vs 38.5%; P<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (P<0.001). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130 or <100 mg/dL at 12 weeks compared to simvastatin (92 and 82% vs 82 and 43%, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo			LDL-C goal <130 or <100 mg/dL at 12 weeks	Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (P=0.53). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups, but were more frequent than with ezetimibe and placebo (13, 14, 9 and 9%, respectively; P values not reported).
Brown et al.[73] (2001) HATS Niacin SR (Slo-Niacin®) titrated to 1 g BID and simvastatin vs antioxidants vs niacin SR (Slo-Niacin®) titrated to 1 g BID, simvastatin, and antioxidants vs placebo Patients whose HDL-C had not increased by prespecified	DB, PC Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) and with ≥3 stenoses of ≥30% of the luminal diameter or 1 stenosis of ≥50%, low HDL-C, normal LDL-C	N=160 3 years	Primary: Changes in lipid profile, arteriographic evidence of change in coronary stenosis (% stenosis caused by most severe lesion in each of nine proximal coronary segments), occurrence of first cardiovascular event (death from coronary causes, MI, stroke or re-vascularization) Secondary: Mean change in % stenosis in lesions of varying degrees of severity, mean change in	Primary: The mean levels of LDL-C, HDL-C, and TG were significantly changed by -42% (P<0.001), 26% (P<0.001) and -36% (P<0.001), respectively, in the niacin plus simvastatin group but were unaltered in the antioxidant only and placebo groups. Similar changes were observed when antioxidants were added to niacin plus simvastatin. The protective increase in HDL_2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (65%) was attenuated by concurrent therapy with antioxidants (28%; P=0.02). The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (P=0.16 compared to placebo) and 0.7% with niacin plus simvastatin plus antioxidants (P=0.004), and regressed by 0.4% with niacin plus simvastatin (P<0.001). The frequency of the composite primary end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebos, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary end point was 90% lower in the niacin plus simvastatin group than placebo (P=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group. Secondary: In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenoses and were supported by the results for the mean minimal luminal diameter.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.			luminal diameter in proximal lesions and all lesions	
Zhao et al.[74] (2004) Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose) vs antioxidants (vitamin E 800 IU/day, vitamin C 1,000 mg/day, beta carotene 25 mg/day and selenium 100 µg/day) vs niacin plus simvastatin plus antioxidants vs placebo	ES Patients with clinical CAD (previous MI, coronary interventions or confirmed angina) including 25 with diabetes with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL	N=160 38 months	Primary: Side effects, response to the question "Overall, how difficult is it to take the study medication?" Secondary: Not reported	Primary: Patients receiving niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo; any degree of flushing (30 vs 23%; P value not significant), symptoms of fatigue, nausea and/or muscle aches (9 vs 5%; P value not significant), AST at least three times the upper limit of normal (3 vs 1%; P value not significant), CPK at least two times the upper limit of normal (3 vs 4%; P value not significant), new onset of uric acid ≥7.5 mg/dL (18 vs 15%; P value not significant) and homocysteine ≥15 µmol/L (9 vs 4%; P value not significant). There were no side effects attributable to the antioxidant regimen. Glycemic control among diabetics declined mildly with niacin plus simvastatin, but returned to pre-treatment levels at month eight and remained stable for the rest of the trial. Niacin plus simvastatin was repeatedly described by 91% of treated patients vs 86% of placebo subjects as "very easy" or "fairly easy" to take. Secondary: Not reported
Stalenhoef et	DB, DD, PG, RCT	N=401	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
al.[75] (2005) COMET Rosuvastatin 10 mg/day for 6 weeks, titrated up to rosuvastatin 20 mg/day for 6 weeks vs atorvastatin 10 mg/day for 6 weeks, titrated up to atorvastatin 20 mg/day for 6 weeks vs placebo daily for 6 weeks, followed with rosuvastatin 20 mg/day for 6 weeks	Patients ≥18 years of age with metabolic syndrome, LDL-C ≥3.36 mmol/L and 10 year CHD risk score of >10%	12 weeks	Percentage change from baseline in LDL-C at six weeks Secondary: Percentage changes from baseline in TC, LDL-C, HDL-C, non-HDL-C at 12 weeks	After six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 mg (41.7 vs 35.7%, respectively; P<0.001) and placebo (42.7 vs 0.3%, respectively; P<0.001). Secondary: After 12 weeks, rosuvastatin 20 mg was associated with a significant reduction in LDL-C compared to atorvastatin 20 mg (48.9 vs 42.5%, respectively; P<0.001). After six and 12 weeks, rosuvastatin was associated with significantly greater improvements in TC (P<0.001), HDL-C (P<0.01) and non-HDL-C (P<0.001) compared to atorvastatin.
Constance et al.[76] (2007) Atorvastatin 20 mg/day vs	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, HbA_{1c} ≤10.0%, ALT/AST levels <1.5 times the upper limit of	N=661 6 weeks	Primary: Change from baseline in LDL-C Secondary: Changes from baseline in TC,	Primary: Across all doses, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (P≤0.001). Secondary: Across all doses, combination therapy was associated with significant reductions in TC, non-HDL, apo B, LDL-C:HDL-C and TC:HDL-C compared to atorvastatin (P≤0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ezetimibe 10 mg/day plus simvastatin 20 or 40 mg/day All patients received atorvastatin 10 mg/day during a 4 week run in period.	normal and CK <1.5 times the upper limit of normal		HDL-C, TG, non-HDL-C, apo B, LDL-C:HDL-C and TC:HDL-C	Combination therapy (simvastatin 40 mg) was associated with a significant reduction in hsCRP compared to atorvastatin (P=0.006). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <2.5 mmol/L compared to atorvastatin (90.5 [10-20 mg], 87.0 [10-40 mg] and 70.4%, respectively; P≤0.001). The incidence of drug-related adverse effects was similar with combination therapy and atorvastatin (0.5 [10-20 mg], 0.5 [10-40 mg] and 2.3%, respectively; P value not reported).
Kumar et al.[77] (2009) Ezetimibe 10 mg/day plus fenofibrate 160 mg/day vs atorvastatin 10 mg/day	RCT, XO Patients with hypercholesterolemia requiring pharmacotherapy	N=43 12 weeks	Primary: Percentage reduction of LDL-C Secondary: Percent changes from baseline in TC, HDL-C and TG	Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (P=0.46). Secondary: Both treatments provided similar improvements in TC (-25.1 vs -24.6%; P=0.806) and HDL-C (10.1 vs 8.9%; P=0.778). Combination therapy showed a trend towards a greater reduction in TGs (25.4 vs 14.5%; P=0.079), although there were no significant difference between the two treatments in terms of the improvement in TC:HDL-C (-29.0 vs -28.7%; P=0.904).
Goldberg et al.[78] (2009) Fenofibric acid 135 mg/day vs atorvastatin 20, 40 or 80 mg/day vs	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 mg/dL, HDL-C <40 mg/dL for men and <50 mg/dL for women and LDL-C ≥130 mg/dL after lipid therapy washout)	N=613 12 weeks	Primary: Percent changes from baseline in TG, HDL-C and LDL-C Secondary: Percent changes from baseline in VLDL-C, TC, apo B and hsCRP; safety	Primary: Combination therapy (atorvastatin 20 mg) resulted in significantly greater improvements in TG (-45.6 vs -16.5%; P<0.001) and HDL-C (14.0 vs 6.3%; P=0.005) compared to atorvastatin 20 mg and LDL-C (-33.7 vs -3.4%; P<0.001) compared to fenofibric acid. Similarly, significantly greater improvements were observed with combination therapy (40 mg) in TG (-42.1 vs -23.2%; P<0.001) and HDL-C (12.6 vs 5.3%; P=0.010) compared to atorvastatin 40 mg and LDL-C (-35.4 vs -3.4%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (20 mg) resulted in significantly higher mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
fenofibric acid 135 mg/day plus atorvastatin 20 or 40 mg/day				percentages of decrease in non-HDL-C compared to fenofibric acid (P=0.026) and in VLDL-C compared to atorvastatin 20 mg (P=0.046). Combination therapy (40 mg) also resulted in significantly higher mean percentage of decrease in non-HDL-C compared to fenofibric acid (P<0.001) and in VLDL-C compared to atorvastatin 40 mg (P<0.001). Improvements in other secondary variables were similar between combination therapy and atorvastatin (TC; P=0.688, apo B; P=0.688 and hsCRP; P=0.074).
Bays et al.[79] (2003) ADVOCATE Niacin ER-lovastatin 1,000-40 mg/day vs niacin ER-lovastatin 2,000-40 mg/day vs simvastatin 40 mg/day vs atorvastatin 40 mg/day	MC, OL, RCT Patients 18 to 70 years of age with 2 consecutive LDL-C ≥160 (if no CAD) or ≥130 mg/dL (with CAD), TG <300 mg/dL and HDL-C <45 (men) or <50 mg/dL (women)	N=315 16 weeks	Primary: Percent change from baseline in LDL-C and HDL-C Secondary: Percent change from baseline in TC, apo B, apo AI, and HDL_2-C and HDL_3-C; median percent change in TG and Lp(a)	Primary: Atorvastatin was associated with a significant 49% reduction in LDL-C compared to a 39, 42 and 39% reduction observed with niacin ER-lovastatin 1,000-40 mg, niacin ER-lovastatin 2,000-40 mg and simvastatin, respectively (P≤0.05 for all). Combination therapy was associated with a significant increase in HDL-C compared to atorvastatin and simvastatin (17, 32, 6 and 7%, respectively; P≤0.05 for all). Secondary: Combination therapy and atorvastatin were associated with significant reductions in TG compared to simvastatin (29, 49, 31 and 19%, respectively; P≤0.05 for all). Combination therapy was associated with a significant reduction in Lp(a) compared to atorvastatin and simvastatin (19, 21, 0 and 2%, respectively; P≤0.05 for all). Combination therapy and simvastatin were associated with significant increases in apo AI compared to atorvastatin (7, 14, 6 and 2%, respectively; P<0.05 for all). Combination therapy (2,000/40 mg) and atorvastatin were associated with significant reductions in apo B compared to combination therapy (2,000/40 mg) and simvastatin (38, 40, 33 and 31%, respectively; P<0.05). Combination therapy was associated with a significant increase in HDL_2-C and HDL_3-C compared to atorvastatin and simvastatin (P<0.05).
Sansanayudh et	OL, PG, RCT	N=100	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
al.[80] (2010) Pitavastatin 1 mg QD vs atorvastatin 10 mg QD	Patients ≥18 years of age with hypercholesterolemia who had an indication for statin therapy according to the NCEP ATP III guidelines	8 weeks	Change from baseline in serum lipid levels Secondary: Proportion of patients who achieved NCEP ATP III LDL-C goal, safety, monthly cost per percent of LDL-C reduction	Both treatments achieved significant reductions in TC and LDL-C (P<0.05). The percentages of reduction in TC and LDL-C with pitavastatin was significantly less compared to atorvastatin (27.55 vs 32.31%; P=0.005 and 37.37 vs 45.75%; P<0.001). Pitavastatin was associated with significant reductions in TG (P=0.001), while atorvastatin was not (P=0.062); however, the changes between the two treatments were not different (P=0.661). Changes in HDL-C were also not significantly different between the two treatments (P=0.294). Secondary: Overall, 79% of all patients achieved their LDL-C goal and there was no significant difference between the two treatments (74 vs 84%; P=0.220). In the high risk category (LDL-C goal <100 mg/dL), there was no difference in the proportion of patients who achieved their LDL-C goal (42.86 vs 71.43%; P=0.127). The possible adverse events of pitavastatin vs atorvastatin included muscle pain (five vs two patients), vertigo (two vs two patients), nausea (three vs one patients), vomiting (one vs one patient), headache (one vs one patient), muscle weakness (one vs zero patients) and stomach ache (zero vs one patients) (P>0.05). During the trial, two patients receiving pitavastatin withdrew from treatment due to an adverse event.
Gumprecht et al.[81] (2011) Atorvastatin 20 mg/day vs pitavastatin 4 mg/day	AC, DB, DD, MC, NI Patients 18 to 75 with type 2 diabetes mellitus (hemoglobin HbA_{1c} ≤7.5% and combined dyslipidemia and TG despite diet modification and oral antidiabetic treatment or insulin	N=418 56 weeks (12 weeks DB, 44 weeks OL extension)	Primary: Change in LDL-C at 12 weeks, proportion of patients achieving LDL-C targets at weeks 16 and 44 and safety and tolerability at 56 weeks Secondary: TC, HDL-C,	Primary: The mean percent change in LDL-C at week 12 was -40.8% for pitavastatin and -43.3% for atorvastatin. The NI analysis of changes in LDL-C at the week 12 did not fulfill the predefined NI criterion since the mean treatment difference for pitavastatin 4 mg compared to atorvastatin 20 mg was -2.33%, outside the lower bound of the 95% CI (-6.18%). A high proportion of patients in the pitavastatin and atorvastatin groups achieved lipid targets during long-term treatment (percentages not reported). Most adverse events were mild or moderate in severity with few discontinuations due to treatment-related adverse events (2.5 and 3.6% for pitavastatin and atorvastatin in the core study, and 2.1 and 1.4%, respectively, in the extension study). One patient in the pitavastatin group died of a MI during the study, which was not considered to be related to the study drug. The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			TG, TC/HDL-C ratio, non-HDL-C, non-HDL-C/HDL-C ratio, apo B, apo AI, apo B: apo AI ratio, hs-CRP, adiponectin LDL, remnant-like particle cholesterol, oxidized LDL and safety	most common adverse events considered to be treatment related were nasopharyngitis and myalgia. The incidence of myalgia during the extension study was slightly lower in the pitavastatin group than in the atorvastatin group (4.2 vs 7.0%, respectively). The incidence of clinically significant elevation of liver enzymes was low in both groups in both the core and extension studies. During the core study, mean blood glucose levels in the pitavastatin group showed a non-significant increase of 2.1% from baseline to week 12. By contrast, mean blood glucose in the atorvastatin group increased significantly from baseline to week 12 by 7.2% (P<0.05). Secondary: Mean TC, TG and non-HDL-C levels decreased from baseline in both the core study and the end of the extension study to a similar degree in both groups. There were no notable between-treatment differences in the observed effects on other lipid parameters such as TC/HDL-C ratio, non-HDL-C/HDL-C ratio and apo B. Pitavastatin and atorvastatin were similar in their effect on increasing HDL-C. By the end of the extension study, more patients receiving pitavastatin had increased their HDL-C levels. Pitavastatin and atorvastatin treatment also reduced CRP, oxidized LDL and increased levels of adiponectin to similar extents.
Yoshitomi et al.[82] (2006) Pitavastatin 1 mg QD vs atorvastatin 10 mg QD	MC, OL Patients ≥18 years of age with hypercholesterolemia (LDL >140 mg/dL and TG <400 mg/dL) treated with or without lipid lowering agents	N=137 12 weeks	Primary: Mean percent reductions from baseline in TC, LDL-C, HDL-C and TG Secondary: Safety	Primary: There were no significant differences between the two treatments in reducing baseline TC (28±8 vs 29±10%) and LDL-C (38±13 vs 41±12%) (P values not reported). There were no differences between the two treatments in increasing baseline HDL-C (3±12 vs 7±12%; P value not reported). Atorvastatin achieved a significantly greater mean percent reduction from baseline in TG compared to pitavastatin (21±25 vs 11±30%; P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Treatment with both pitavastatin and atorvastatin was well tolerated. No serious adverse event was associated with the treatment. No adverse events of musculoskeletal, renal or hepatocellular toxicity occurred and no patient had an elevation of the CK level that was >3 times the upper limit of normal.
Lee et al.[83] (2007) Pitavastatin 2 mg QD vs atorvastatin 10 mg QD Patients who did not achieve the LDL-C goal by week 4 received a double dose of the assigned medications for an additional 4 weeks.	MC, OL, RCT Patients 20 to 79 years of age with untreated hypercholesterolemia, fasting TG <400 mg/dL and a LDL-C >130 mg/dL after a 4 week dietary lead in period	N=268 8 weeks	Primary: Changes from baseline in lipid parameters and hsCRP Secondary: Tolerability	Nine (8.2%) patients receiving pitavastatin and 12 (10.7%) patients receiving atorvastatin did not achieve the LDL-C goal by week four and received a double dose of their assigned medication for the remaining four weeks. Primary: There was no significant difference between the two treatments in the proportion of patients achieving the LDL-C goal at eight weeks (92.7 vs 92.0%; P value not reported). There was no difference between the two treatments in terms of the mean percent changes in LDL-C (-42.9 vs -44.1%), TC (-28.0 vs -29.6%), TG (-9.9 vs -11.0%), HDL-C (7.1 vs 6.7%) and hsCRP (-23.9 vs -15.4%) (P values not reported). Secondary: Both treatments were well tolerated and 21 adverse reactions considered related to study medication occurred in 14 patients receiving pitavastatin and 23 occurred in 19 patients receiving atorvastatin. There were no clinically relevant changes in laboratory values.
Sasaki et al.[84] (2008) Pitavastatin 2 mg QD vs atorvastatin 10 mg QD	MC, OL, PG, RCT Patients ≥20 years of age with LDL-C ≥140 mg/dL, HDL-C <80 mg/dL, TG <500 mg/dL and glucose intolerance	N=189 52 weeks	Primary: Percent change from baseline in serum HDL-C Secondary: Percent change from baseline in LDL-C, non-HDL-C, LDL-C:HDL-C, TG,	Primary: Pitavastatin was associated with an increase in HDL-C of 8.2%, which was significantly greater than atorvastatin (2.9%; P=0.031). Secondary: Atorvastatin was associated with significant reductions LDL-C (-40.1 vs -33.0%; P=0.002), non-HDL-C (-37.4 vs -31.1%; P=0.004), apo B (-35.1 vs -28.2%; P<0.001) and apo E (-28.1 vs -17.8%; P<0.001) compared to pitavastatin. There were no differences between the two treatments in terms of changes in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			apo AI, apo B, apo B:AI and apo E; tolerability	LDL-C:HDL-C, apo B:AI and TG. Apo AI increased significantly more with pitavastatin compared to atorvastatin (5.1 vs 0.6%; P=0.019). Effects on glucose metabolism were similar between the two treatments, measured by fasting plasma insulin, FPG and HbA_{1c}. Initiation of medication use for the treatment of diabetes occurred at a similar rate with both treatments (11%). Adverse events occurred at a similar rate between the two treatments.
Saito et al.[85] (2002) Pitavastatin 2 mg/day vs pravastatin 10 mg/day	DB, MC, PG, RCT Patients 20 to 75 years of age with primary hyperlipidemia (TC ≥200 mg/dL and TG <400 mg/dL)	N=240 12 weeks	Primary: Mean percent changes from baseline in TC, LDL-C and TG Secondary: Mean percent changes from baseline in apo B, apo CII, apo CIII and apo E; safety	Primary: Pitavastatin achieved significantly greater mean percent reductions from baseline in TC and LDL-C (28.2 and 37.6%) compared to pravastatin (14.0 and 18.4%; both P<0.001). In cases of a baseline TG level ≥150 mg/dL, the mean percent reduction of TG with pitavastatin (23.3%) showed non-inferiority to that observed with pravastatin (20.2%; P=0.024). Secondary: Mean percent reductions in apo B, apo CII, apo CIII and apo E with pitavastatin (33.8, 15.7, 9.5 and 22.9%) were significantly greater compared to pravastatin (16.9, 6.1, 2.6 and 12.6%; P values not reported). The adverse event profile was similar for both treatments and neither treatment caused clinically relevant laboratory abnormalities. Three patients receiving pitavastatin and two patients receiving pravastatin withdrew from the study due to adverse events considered to be drug-related.
Stender et al.[86] (2013) Pitavastatin (1, 2, or 4 mg) vs pravastatin (10, 20, or 40 mg)	DB, PG, RCT Elderly (≥65 years of age) patients with primary hypercholesterolemia or mixed dyslipidemia with LDL-C between 130 mg/dL and	N=942 12 week treatment period (6 to 8 week wash-out/dietary period before randomization)	Primary: Percentage change in LDL-C from baseline Secondary: Other lipid parameters; safety	Primary: Mean LDL-C concentrations fell from baseline to endpoint in a dose-dependent manner in all treatment groups. Pitavastatin met the primary endpoint of non-inferiority in LDL-C reduction compared with pravastatin at all dose comparisons (low-dose group, pitavastatin 1 mg vs pravastatin 10 mg; intermediate-dose group, 2 mg vs 20 mg; and higher-dose group, 4 mg vs 40 mg). Secondary: Plasma concentrations of TC, non-HDL-C, oxidized LDL-C, the non-HDL-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	220 mg/dL despite dietary therapy			C:HDL-C ratio, the TC:HDL-C ratio, Apo-B and the Apo-B:Apo-A1 ratio decreased significantly more with pitavastatin than with pravastatin. The percentage of patients who reported at least one treatment-emergent adverse event (TEAE) was comparable between groups and ranged from 49.0 to 55.3%. There was no indication of a relationship between TEAE incidence and dose.
Park et al.[87] (2005) Pitavastatin 2 mg QD vs simvastatin 20 mg QD	MC, OL, Phase III, PRO, RCT Patients 20 to 75 years of age with hypercholesterolemia, fasting TG <600 mg/dL and LDL-C >130 mg/dL after a 4 week dietary lead in period	N=104 8 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean percent change from baseline in TC, TG and HDL-C; safety	Primary: There was no significant difference between the two treatments in the reduction in LDL-C (11.6 vs 12.9%; P=0.648). Secondary: There were no significant differences between the two treatments in the changes in TC (-8.9 vs -8.7%; P=0.405), TG (-20.6 vs 36.9%; P=0.147), or HDL-C (13.4 vs 16.2%; P=0.127). No serious adverse events were observed in either treatment. One patient receiving pitavastatin and four patients receiving simvastatin had to discontinue the study medication due to adverse events. Elevations in CK greater than two times upper limit of normal were observed in 3.8 and 9.8% of pitavastatin- and atorvastatin-treated patients (P=0.269). Mild elevations in AST less than two fold times upper limit of normal was observed in one patient receiving simvastatin.
Ose et al.[88] (2009) Pitavastatin 2 or 4 mg/day vs simvastatin 20 or 40 mg/day	AC, DB, DD, PRO, RCT Patients diagnosed with either primary hypercholesterolemia or combined dyslipidemia	N=857 12 weeks	Primary: Changes in lipid panel Secondary: Safety profiles	Primary: Pitavastatin 2 mg was associated with a significant improvement in LDL-C, non-HDL-C and TC compared to simvastatin 20 mg (P=0.014, 0.021 and 0.041 respectively). LDL-C was reduced by 39% with pitavastatin 2 mg compared to 35% with simvastatin 20 mg. Pitavastatin 4 mg and simvastatin 40 mg had similar effects on the lipid panel. Reductions in LDL-C were 44% with pitavastatin 4 mg and 43% for simvastatin 40 mg. Secondary: Safety profiles were similar at all dose levels.
Eriksson et al.[89] (2011)	AC, DB, DD, MC, NI, PG, RCT	N=355	Primary: Percentage	Primary: The mean LDL-C concentrations decreased from baseline by -44.0% with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Pitavastatin 4 mg/day vs simvastatin 40 mg/day	Patients 18 to 75 years of age with primary hypercholesterolemia or combined dyslipidemia that was uncontrolled (LDL-C ≥130 mg/dL and ≤5,220 mg/dL; TG ≤400 mg/dL) despite dietary measures, and at least two cardiovascular risk factors	12 weeks	change in LDL-C from baseline Secondary: Proportion of patients reaching LDL-C targets, percentage changes from baseline in concentrations of TG, TC, HDL-C, non-HDL-C, apo B and apo AI, and absolute changes from baseline in concentrations of oxidized LDL, CRP and ratios of TC:HDL-C, non-HDL:HDL-C, and apo B/apo A1 and safety	pitavastatin compared to -43.8% with simvastatin. The adjusted mean treatment difference was 0.31%, which was within the predefined limits of NI (95% CI, -2.47 to 3.09; P=0.829). Secondary: There was no statistically significant difference in the proportion of patients achieving NCEP LDL-C targets (87.1 vs 85.6%; P=0.695) or EAS LDL-C targets (87.1 vs 81.4%; P=0.170) between patients treated with pitavastatin or simvastatin. Pitavastatin provided a significantly greater reduction in triglycerides compared to simvastatin (-19.8 vs -14.8%; P=0.044), as well as a greater increase in HDL-C with pitavastatin (6.8 vs 4.5%), which was not statistically significant (P=0.083). There were no other significant differences in secondary lipid measures between the two groups. Treatment-emergent adverse events occurred in 51.1% of patients receiving pitavastatin and 50.4% of patients receiving simvastatin. The most commonly reported treatment-emergent adverse events were headache, nasopharyngitis, constipation, myalgia and back pain.
Rosenson et al.[90] (2009) Rosuvastatin 10 mg QD for 6 weeks, followed by 20 mg thereafter	DB, MC, PC, RCT Patients ≥18 years of age with the metabolic syndrome, LDL-C 130 to 250 mg/dL and a 10-year CHD risk score >10%	N=318 12 weeks	Primary: Lipoprotein particle concentrations Secondary: Not reported	Primary: After six weeks of therapy, rosuvastatin 10 mg and atorvastatin 10 mg significantly reduced LDL-C, LDL particle concentration, apo B, and non-HDL-C compared to placebo (P<0.001). Rosuvastatin significantly reduced LDL-C (P<0.001), LDL particle concentration (P<0.05), and non-HDL-C (P<0.01) compared to atorvastatin after six and 12 weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 10 mg QD for 6 weeks, followed by 20 mg thereafter vs placebo				After six weeks of therapy, rosuvastatin 10 mg and atorvastatin 10 mg significantly reduced VLDL particle concentration and serum triglycerides compared to placebo (P<0.001). There was no difference between the two statins on either end point at week 6 or 12. After six weeks of therapy, rosuvastatin 10 mg increased HDL particle concentration (15%) and HDL-C (10%) compared to placebo (P<0.001). Atorvastatin significantly increased HDL particle concentration compared to placebo (6%, P=0.013); however, there was no difference in HDL-C (4%, P=0.45). Rosuvastatin significantly increased HDL particle concentration and HDL-C compared to atorvastatin after six and 12 weeks (P≤0.002). Neither statin showed a significant effect on apo AI compared to placebo; however, increases in apo AI were significantly greater with rosuvastatin than atorvastatin at six and 12 weeks (P=0.001 and P=0.02, respectively). A higher proportion of patients receiving rosuvastatin achieved LDL-C <100 mg/dL compared to atorvastatin at six and 12 weeks (P<0.01 and P<0.0001, respectively). Patients receiving rosuvastatin achieved LDL particle concentration <1,300 nmol/L at 12 weeks (P=0.02) and <1,000 nmol/L at six weeks (P=0.02) compared to atorvastatin. The percentage of patients who attained LDL particle concentration <1,300 nmol/L was similar to that achieving LDL-C <100 mg/dL. Secondary: Not reported
Park et al.[91] (2010) Rosuvastatin 10 mg/day vs atorvastatin 10	MC, OL, PG Patients ≥18 years of age with nondiabetic metabolic syndrome and hypercholesterolemia	N=351 6 weeks	Primary: Percent change from baseline in TC, LDL-C, HDL-C, TG, non-HDL-C, apo AI and apo B; proportion of patients	Primary: After six weeks, significantly greater reductions in TC (35.94±11.38 vs 30.07±10.46%; P<0.001), LDL-C (48.04±14.45 vs 39.52±14.42%; P<0.001), non-HDL-C (42.93±13.15 vs 35.52±11.76%; P<0.001) and apo B (38.7±18.85 vs 32.57±17.56%; P=0.002) were achieved with rosuvastatin compared to atorvastatin. No differences between treatments were observed in changes in HDL-C (P=0.448), TG (P=0.397) and apo AI (P=0.756).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day			achieving NCEP ATP III LDL-C goals (<100, <130 and <160 mg/dL); change from baseline in metabolic parameters; safety Secondary: Not reported	Overall, the proportion of patients achieving the LDL-C goals was significantly greater with rosuvastatin compared to atorvastatin (87.64 vs 69.88%; P<0.001). Corresponding proportions for the LDL-C goals <100, <130 and <160 mg/dL were: 82.7 vs 59.2 (P<0.001), 94.3 vs 84.2 (P=0.032) and 96.8 vs 97.3% (P=0.990). Changes in glucose (P=0.231), insulin (P=0.992), HbA_{1c} (P=0.456) and HOMA index (P=0.910) were not significantly different between the two treatments. The safety and tolerability of the two treatments were similar. Secondary: Not reported
Mazza et al.[92] (2008) Rosuvastatin 10 mg QD vs atorvastatin 20 mg QD	OL, RCT Patients 18 to 65 years of age with primary hypercholesterolemia (LDL-C >200 mg/dL) and at high risk for CHD	N=106 48 weeks	Primary: Plasma levels of TC, TG, LDL-C HDL-C, non-HDL-C Secondary: Not reported	Primary: After 48 weeks of treatment, atorvastatin significantly lowered TC, LDL-C, and non HDL-C levels (-21.6; -30; -26.98%, respectively; P<0.001 combined). HDL-C levels increased 4.52% (P value not significant) TG levels decreased 4.62% (P value not significant). After 48 weeks of treatment, rosuvastatin significantly lowered TC, LDL-C, non HDL-C, and TG levels (-35.77, -44.32, -43.12, -36.41%, respectively; P<0.001 combined). HDL-C level also decreased -2.04% (P value not significant). Rosuvastatin was more effective than atorvastatin in reducing plasma levels of TC, LDL-C, non-HDL-C and TG (-35.77, -44.32, -43.12, -36.41%, respectively, with rosuvastatin vs -21.62, -30, -26.98, -4.62%, respectively, with atorvastatin; P<0.005). Both drugs had no significant effect on plasma HDL-C levels relative to baseline. There were no significant differences in either treatment group in parameters related to safety. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Betteridge et al.[93] (2007) ANDROMEDA Rosuvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks vs atorvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks All patients were randomized after a 4 week dietary lead in period.	DB, MC, PG, RCT Patients ≥18 years of age with type 2 diabetes, ≥2 FPG levels of ≥7 mmol/L and TG ≤6 mmol/L	N=509 16 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Percentage changes from baseline in LDL-C, TC, HDL-C, TG, non-HDL-C, cholesterol ratios, apo B, apo ratio and HbA_{1c}; proportion of patients achieving 2003 Joint European Societies LDL-C (<2.5 mmol/L) and TC (<4.5 mmol/L) goals	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (57.4 vs 46.0%; P=0.001). Secondary: Rosuvastatin was associated with a significant reduction in apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C and apo B compared to atorvastatin (P<0.001). Rosuvastatin was associated with a significant reduction in HbA_{1c} compared to atorvastatin (P=0.049). A significantly greater proportion of patients receiving rosuvastatin achieved LDL-C goals compared to patients receiving atorvastatin (95.6 vs 87.3%; P=0.002). A significantly greater proportion of patients receiving rosuvastatin achieved TC goals compared to patients receiving atorvastatin (93.4 vs 86.0%; P=0.01).
Betteridge et al.[94] (2007) ANDROMEDA Rosuvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks	Subanalysis of ANDROMEDA Patients ≥18 years of age with type 2 diabetes, ≥2 FPG levels of ≥7 mmol/L and TG of ≤6 mmol/L	N=509 16 weeks	Primary: Composite of changes from baseline in hsCRP <2 mg/L and LDL-C <70 mg/dL Secondary: Not reported	Primary: Rosuvastatin was associated with a significant reduction in the primary endpoint compared to atorvastatin (58 vs 37%; P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks All patients were randomized after a 4 week dietary lead in period.				
Clearfield et al.[95] (2006) PULSAR Rosuvastatin 10 mg QD vs atorvastatin 20 mg QD	MC, OL, PG, RCT Patients ≥18 years of age with hypercholesterolemia and either a history of CHD or a CHD risk equivalent, with the mean of the 2 most recent LDL-C (within 15% of each other) ≥130 to <220 mg/dL, as well as TG <400 mg/dL	N=996 6 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving the NCEP ATP III and the 2003 European LDL-C goals (<100 mg/dL), the 2003 European LDL-C goal for patients at greatest risk, the NCEP ATP III non-HDL-C goal (<130 mg/dL),	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (42.7 vs 44.6%; P<0.05). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved NCEP ATP III and the 2003 European LDL-C goals compared to patients receiving atorvastatin (68 vs 63%; P<0.05). In addition, a significantly greater proportion of high risk CHD patients receiving rosuvastatin achieved the 2003 European LDL-C goals compared to high risk CHD patients receiving atorvastatin (65.6 vs 60.3%; P>0.05). A nonsignificant greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III non-HDL-C goal compared to patients receiving atorvastatin (69.7 vs 65.0%; P>0.05). A nonsignificant greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III combined LDL-C:TC goal compared to atorvastatin (55.2 vs 53.3%; P>0.05). Rosuvastatin was associated with a significant increase in HDL-C compared to atorvastatin (6.4 vs 3.1%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			combined LDL-C:TC goal <175 to 190 mg/dL; percentage changes from baseline in HDL-C, TC, TG, non-HDL-C, apo B, LDL-C:HDL-C, TC:HDL-C, non-HDL-C:HDL-C and Lp(a); safety	There was no difference in the changes of TC, TG, non-HDL-C and apo B observed with rosuvastatin and atorvastatin (P>0.05). Rosuvastatin was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin (47.6 vs 44.0%; P<0.001). Rosuvastatin was associated with a significant reduction in TC:HDL-C compared to atorvastatin (34.6 vs 32.3%; P<0.01). Rosuvastatin was associated with a significant reduction in non-HDL-C:HDL-C compared to atorvastatin (43.3 vs 40.2%; P<0.001). Atorvastatin was associated with a significant increase in Lp(a) compared to rosuvastatin (13.3 vs 2.1%; P<0.001). The frequency and type of adverse events were similar with both treatments (27.5 vs 26.1%; P value not reported). The most commonly reported adverse effects were myalgia and urinary tract infections.
Deedwania et al.[96] (2007) IRIS Rosuvastatin 10 or 20 mg/day vs atorvastatin 10 or 20 mg/day All patients were randomized after a 6 week dietary lead in period.	MC, OL, RCT South-Asian patients ≥18 years of age with CHD or CHD risk equivalent and LDL-C ≥100 mg/dL or ≥2 risk factors, 10 year CHD risk 10 to 20% and LDL-C ≥130 mg/dL or 0 to 1 risk factor and LDL-C ≥160 mg/dL, with TG <500 mg/dL	N=740 6 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving NCEP ATP III LDL-C goals; percentage change from baseline in non-HDL-C, HDL-C, TC and TG; safety	Primary: At six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 mg (P=0.0023). The difference in LDL-C reduction from baseline at six weeks between rosuvastatin 20 mg and atorvastatin 20 mg was not significant (P value not reported). Secondary: The proportion of patients achieving NCEP ATP III LDL-C goals was similar with rosuvastatin 10 and 20 mg and atorvastatin 10 and 20 mg (79, 89, 76 and 85%, respectively; P value not reported). At six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin 10 mg (P<0.017). There were no clinically relevant differences between treatments in adverse events or incidence of CK >10 times the upper limit of normal, ALT >3 times the upper limit of normal, proteinuria or hematuria.
Ferdinand et al.[97]	OL, RCT	N=774	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2006) ARIES Rosuvastatin 10 or 20 mg QD vs atorvastatin 10 or 20 mg QD All patients were randomized after a 6 week dietary lead in period.	African American patients ≥18 years of age with LDL ≥160 to ≤300 mg/dL, TG <400 mg/dL	6 weeks	The change from baseline in LDL-C Secondary: Changes from baseline in other lipid parameters	Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (P<0.017). Secondary: Rosuvastatin was associated with a significant reduction in TC, non-HDL-C, apo B and lipoprotein and apo ratios compared to atorvastatin (P<0.017). Rosuvastatin was associated with a significant increase in HDL-C compared to atorvastatin (P<0.017). Adverse events were similar with rosuvastatin and atorvastatin (34.4 and 33.6%, respectively; P value not reported).
Lloret et al.[98] (2006) STARSHIP Rosuvastatin 10 or 20 mg QD vs atorvastatin 10 or 20 mg QD All patients were randomized after a 6 week dietary lead in period.	MC, OL, RCT Hispanic American patients ≥18 years of age with a 10 year risk >10% for CHD, current CHD or its equivalent, LDL ≥130 to ≤300 mg/dL on 2 measurements within 15% of each other, TG <400 mg/dL	N=696 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Proportion of patients achieving NCEP ATP III lipid goals; percent change from baseline in TC, apo B, non-HDL-C, TG, HDL, apo AI, LDL-C:HDL-C, TC:HDL-C and apo B:apo AI; safety	Primary: Rosuvastatin 10 and 20 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 and 20 mg (45, 50, 36 and 42%, respectively; P<0.0001). Secondary: A greater proportion of patients receiving rosuvastatin 10 and 20 mg achieved LDL-C goals compared to atorvastatin 10 and 20 mg (78, 88, 60 and 73%, respectively; P value not reported). Rosuvastatin 10 and 20 mg was associated with a significant reduction in TC compared to atorvastatin 10 and 20 mg (10 mg; P<0.0001, 20 mg; P<0.01, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in apo B compared to atorvastatin 10 and 20 mg (10 mg; P<0.0001, and 20 mg; P<0.017, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin 10 and 20 mg, respectively, at six months (P<0.0001 for both, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Rosuvastatin 10 and 20 mg was associated with a significant reduction in TC:HDL-C compared to atorvastatin 10 and 20 mg (10 mg; P<0.0001, 20 mg; P<0.01, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in non-HDL-C:HDL-C compared to atorvastatin 10 and 20 mg (10 mg; P<0.0001, 20 mg; P<0.01, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in apo B:apo AI compared to atorvastatin 10 and 20 mg (P<0.01 for both, respectively). Adverse events were similar between treatments (P value not reported). There were no cases of myopathy, rhabdomyolysis or clinically significant increases in serum CK.
Milionis et al.[99] (2006) ATOROS Rosuvastatin 10 mg QD for 6 weeks, titrated to 20 mg/day vs atorvastatin 20 mg QD for 6 weeks, titrated to 40 mg/day All patients were randomized after a 6 week dietary lead in period.	OL, PG, RCT Adult patients free of symptomatic ischemic heart disease or any other clinically evident heart disease, at moderate risk for CHD according to NCEP ATP classification, with baseline TC >240 mg/dL and TG <350 mg/dL	N=180 24 weeks	Primary: Proportion of patients achieving the NCEP ATP III LDL-C goal (<130 mg/dL) Secondary: Changes from baseline in LDL-C, HDL-C, TC, TG, non-HDL-C and apo B	Primary: After six weeks, 75.0 and 71.7% of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin and atorvastatin, respectively (P value not reported). Secondary: Both rosuvastatin and atorvastatin were associated with significant reductions in LDL-C (48.7 vs 44.6%; P<0.001). Rosuvastatin was associated with a significant five percent increase in HDL-C (P<0.001). Atorvastatin was associated with a significant 2.1% reduction in HDL-C (P<0.001). Compared to atorvastatin, rosuvastatin was associated with a significantly greater increase in HDL-C (P=0.002). Both rosuvastatin and atorvastatin were associated with significant reductions in TC (36.1 vs 36.9%; P<0.001). Both rosuvastatin and atorvastatin were associated with significant reductions in TG (29.0 vs 27.8%; P<0.001). Both rosuvastatin and atorvastatin were associated with significant reductions in non-HDL-C (45 vs 46%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Both rosuvastatin and atorvastatin were associated with significant reductions in apo B (29 vs 26%; P<0.001). The incidence of myalgia was similar with both treatments (3%; P value not reported). There were no reports of significant ALT or CK elevations.
Ai et al.[100] (2008) STELLAR Rosuvastatin 40 mg/day vs atorvastatin 80 mg/day	OL Patients ≥18 years of age with hypercholesterolemia, LDL-C ≥160 to <250 mg/dL and TG <400 mg/dL	N=271 6 weeks	Primary: Changes from baseline in direct LDL-C and small dense LDL-C Secondary: Percentage changes from baseline in HDL-C, TC, TG, non-HDL-C and TC:HDL-C	Primary: Rosuvastatin was associated with a significant reduction from baseline in direct LDL-C compared to atorvastatin (52 vs 50%; P=0.01). Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared to atorvastatin (53 vs 46%; P<0.001). Secondary: Rosuvastatin was associated with a significant increase from baseline in HDL-C compared to atorvastatin (10 vs 2%; P<0.001). There was no difference between treatments in TC (P=0.10) and TG (P=0.50) reductions. Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin (51 vs 48%; P<0.0078). Rosuvastatin was associated with a significant reduction in TC:HDL-C compared to atorvastatin (46 vs 39%; P<0.001).
Leiter et al.[101] (2007) POLARIS Rosuvastatin 40 mg QD vs atorvastatin 80 mg QD	DB, PG, RCT Patients 45 to 80 years of age with hypercholesterolemia and a history of CHD, clinical evidence of atherosclerosis or a 10 year Framingham CHD risk score >20%,	N=871 26 weeks	Primary: The percentage change from baseline in LDL-C levels at week eight Secondary: Percentage change from baseline in LDL-C levels at week 26,	Primary: After eight weeks, rosuvastatin was associated with a significantly greater reduction in LDL-C compared to atorvastatin (56 vs 52%; P<0.001). Secondary: After 26 weeks, rosuvastatin was associated with a significantly greater reduction in LDL-C compared to atorvastatin (57 vs 53%; P value not reported). After eight weeks, rosuvastatin was associated with a significantly greater reduction in TG (27.0 vs 22.2%; P<0.05), non-HDL-C (50.8 vs 48.3%; P<0.01), LDL-C:HDL-C (58.5 vs 53.6%; P<0.001), TC:HDL-C (44.4 vs 41.1%; P<0.001), non-HDL-C:HDL-C (53.6 vs 49.6%; P<0.001), apo B (44.6

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	with LDL-C ≥160 to <250 mg/dL and TG <400 mg/dL		percentage change from baseline in other lipids and lipoproteins at weeks eight and 26, proportion of patients achieving NCEP ATP III and 2003 European lipid goals at eight and 26 weeks, safety	vs 42.3%; P<0.05) and apo AI (4.2 vs -0.5%; P<0.001) compared to atorvastatin. After eight weeks, rosuvastatin was associated with a significantly greater increase in HDL-C compared to atorvastatin (9.6 vs 4.4%; P<0.001). After six weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III LDL-C goals of <100 (80 vs 72%; P<0.01) and <70 mg/dL (36 vs 18%; P<0.001) compared to patients receiving atorvastatin. After six weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the 2003 European lipid goals compared to patients receiving atorvastatin (79 vs 69%; P<0.001). The incidence of drug-related adverse events was low with both treatments (0.5 vs 0.2%; P value not reported).
Wolffenbuttel et al.[102] (2005) CORALL Rosuvastatin 10 mg QD for 6 weeks, titrated to 20 mg QD for 6 weeks, titrated to 40 mg QD for 6 weeks vs atorvastatin 20 mg QD for 6 weeks, titrated to 40 mg QD for 6 weeks, titrated to	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥3 months, LDL ≥3.36 mmol/L in statin naïve patients or LDL 2.99 to 5 mmol/L in patients exposed to statin therapy within the previous 4 weeks, TG <4.52 mmol/L and HbA_{1c} <10.0%	N=265 24 weeks	Primary: Reduction in LDL-C, HDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B; percentage of patients who achieved LDL-C goals (<2.6 or <2.5 mmol/L) at 18 weeks Secondary: Not reported	Primary: Rosuvastatin and atorvastatin were associated with significant reductions from baseline in LDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B (P<0.001). Rosuvastatin was associated with significant reduction in LDL-C (P<0.01), apo ratio (P<0.05), LDL-C:HDL-C (P<0.01), TC (P<0.05), TC:HDL-C (P<0.05), non-HDL-C (P<0.05) and apo B (P<0.05) compared to atorvastatin. A significantly greater percentage of patients receiving rosuvastatin achieved LDL-C goals at 18 weeks compared to patients receiving atorvastatin (P<0.05). The incidence of treatment-related adverse events was similar between the two treatments (47 vs 50%, respectively; P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
80 mg QD for 6 weeks All patients were randomized after a 6 week dietary lead in period.				
Bullano et al.[103] (2007) Rosuvastatin (mean daily dose, 11 mg) vs atorvastatin (mean daily dose, 15 mg)	RETRO Patients ≥18 years of age, initiated on rosuvastatin or atorvastatin between August 1, 2003 and September 30, 2004 with ≥1 lipid level (LDL-C, TG, HDL-C, TC) obtained prior to and after therapy initiation	N=453 Up to 79 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), percentage change from baseline in HDL-C, TC, TG and non-HDL-C	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (35 vs 26%; P<0.001). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved NCEP ATP III LDL-C goals compared to atorvastatin, when adjusted for age, sex, LDL-lowering required to reach goal, risk category and duration of therapy (74 vs 65%; P<0.05). Unadjusted attainment rates were similar with both treatments (P=0.088). Patients receiving rosuvastatin required greater LDL-C reduction to reach their LDL-C goal compared to patients receiving atorvastatin (26.3 vs 23.5%; P<0.05). In addition, significantly more patients receiving rosuvastatin reached the updated, optional NCEP ATP III LDL-C goals compared to patients receiving atorvastatin (61 vs 48%; P<0.05). There was no difference between the two treatments in the change in HDL-C (P=0.234). Rosuvastatin was associated with a greater reduction in TC compared to atorvastatin (26 vs 20%; P<0.001). There was no difference between the two treatments in the change in TG (P=0.192). Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin (33 vs 25%; P<0.001).
Wlodarczyk et al.[104] (2008)	MA (25 head-to-head RCTs) Patients with	N=19,621 Mean 8.6 weeks (range, 4 to 12	Primary: Change from baseline in LDL-C	Primary: At equivalent doses, rosuvastatin produced significantly larger reductions in LDL-C compared to atorvastatin (mean treatment difference, -8.52%; 95% CI, -9.23 to -7.81) or a two times higher atorvastatin dose (-3.24%; 95% CI, -4.10

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Rosuvastatin 5, 10, 20 or 40 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day	hypercholesterolemia	weeks)	Secondary: Safety	to -2.38). No difference between the two treatments were observed when rosuvastatin was compared to a four times higher atorvastatin dose (1.12%; 95% CI, -0.24 to 2.48). Results were similar for DB and OL trials. The percentage of LDL-C decrease associated with rosuvastatin ranged from 41.0 to 56.0% for the 5 and 40 mg dosing regimens, respectively. Atorvastatin ranged from 37.2 to 51.3% for the 10 and 80 mg dosing regimens. Secondary: Event rates for myalgia ranged from 3.5 to 4.2% for atorvastatin 80 mg and rosuvastatin 5 mg. No clear dose-response relation was evident for either treatment and no difference between the two treatments was noted. Rates of withdrawal were low, ranging from 4.1 to 6.4% for rosuvastatin 5 mg and atorvastatin 40 mg. Rates due to adverse events were similar between the two treatments. At the 1:1 dose ratio, the trend toward a higher rate with rosuvastatin did not reach significance (OR, 1.258; 99% CI, 0.972 to 1.627). This trend was no longer evident when only DB trials were included (OR, 0.89; 95% CI, 0.48 to 1.63). Serious adverse events tended to be lower with rosuvastatin at each dose ratio, but there was no strong evidence of a treatment effect. There were nine patients with CK >10 times the upper limit of normal and 23 deaths were reported. Rates of ALT greater than three times the upper limit of normal were highest with atorvastatin 80 mg (2.2/100 patients) and rosuvastatin 40 mg (0.8/100 patients). Within treatment MA showed that GFR tended to increase with atorvastatin and rosuvastatin by 3.8% (99% CI, 2.77 to 4.77) and 2.7% (99% CI, 1.79 to 3.58). No difference was noted between the two treatments.
Fox et al.[105] (2007) Rosuvastatin vs	RETRO Adult patients ≥18 years of age switching to either rosuvastatin or	N=277 Patients received statin therapy between August 2003 and March	Primary: Percent reduction from baseline in LDL-C	Primary: A switch to rosuvastatin was associated with a significant reduction in LDL-C compared to a switch to simvastatin (18.5 vs 5.8%; P<0.05). A significantly greater proportion of patients who switched to rosuvastatin achieved a LDL-C reduction >25% compared to those who switched to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin	simvastatin from another statin between August 2003 and March 2006, not receiving other antidyslipidemic medications in the 12 months before or after initiating statin therapy	2006	Secondary: Not reported	simvastatin (44 vs 29%; P<0.05). Patients who switched from atorvastatin to rosuvastatin experienced a significantly greater reduction in LDL-C compared to those who switched to simvastatin therapy (14.6 vs 4.6%; P<0.05). Secondary: Not reported
Bullano et al.[106] (2006) Rosuvastatin 5 to 40 mg/day vs other statins (atorvastatin 10 to 80 mg/day, simvastatin 5 to 80 mg/day, pravastatin 10 to 80 mg/day, lovastatin 10 to 80 mg/day and fluvastatin 20 to160 mg/day)	RETRO Patients ≥18 years of age initiated on a statin between August 1, 2003 and September 30, 2004 with ≥1 LDL-C level obtained prior to and after therapy initiation	N=8,251 Up to 122 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), percentage change from baseline in HDL-C, TC and TG	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to other statins (33 vs 24 [atorvastatin], 20 [simvastatin], 18 [pravastatin], 13 [fluvastatin] and 16% [lovastatin]; P<0.05). Rosuvastatin 10 mg/day was associated with a significantly greater reduction in LDL-C compared to atorvastatin 10 to 20 mg/day (P<0.05) or simvastatin 10 to 20 mg/day (P<0.05). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III LDL-C goals compared to patients receiving other statins (P<0.05). Patients receiving rosuvastatin required greater LDL-C reduction to reach their LDL-C goal compared to patients treated with other statins (29 vs 23 to 27%; P<0.05). A significantly greater proportion of patients receiving rosuvastatin achieved the updated, optional NCEP ATP III LDL-C goals compared to patients receiving other statins (58 vs 29 to 48%; P<0.05). There was no difference between rosuvastatin and other statins in HDL-C reductions (P>0.05). Rosuvastatin was associated with a significant reduction in TC compared to other statins (24% vs 18 [atorvastatin], 14 [simvastatin], 13 [pravastatin], 10 [fluvastatin] and 13% [lovastatin]; P<0.05). Rosuvastatin was associated with a significant reduction in TG compared to other statins (11% vs 6 [simvastatin], 4 [pravastatin], 4 [fluvastatin] and 5%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				[lovastatin]; P<0.05). There was no difference in TG reduction between rosuvastatin and atorvastatin (11 vs 10%; P>0.05).
Nicholls et al.[107] (2010) VOYAGER Rosuvastatin (variable doses) vs atorvastatin (variable doses) vs simvastatin (variable doses)	MA (37 trials) Patients with hypercholesterolemia	N=32,258 Variable duration	Primary: Impact of increasing dose on lowering LDL-C, TG, non-HDL-C, and apo B Secondary: Not reported	Primary: Increasing doses of all agents resulted in an incremental benefit on LDL-C reduction. The incremental impact of dose doubling was comparable, with a 5% to 7% increase in LDL-C lowering. A greater percentage of patients achieved LDL-C treatment goals using increasing doses of all agents, as well as in patients with lower cholesterol levels at baseline. Increasing doses of all agents resulted in an incremental benefit on TG reduction. The incremental impact of dose doubling was comparable, with a 2 to 4% increase in TG lowering. Increasing doses of all agents resulted in an incremental benefit on non-HDL-C reduction. The incremental impact of dose doubling was comparable, with a 4 to 6% increase in non-HDL-C lowering. Increasing doses of all agents resulted in an incremental benefit on apo B reduction. The incremental impact of dose doubling was comparable, with a 4 to 6% increase in apo B lowering. Increasing statin dose was not associated with an increase in withdrawal rates due to adverse events. Secondary: Not reported
Harley et al.[108] (2007) Rosuvastatin, after simvastatin therapy vs	RETRO Adult patients ≥18 years of age, receiving simvastatin monotherapy between July 2005 and June 2006,	N=134,160 1 year	Primary: Percentage of patients achieving NCEP ATP III LDL goal after switching from simvastatin to another statin	Primary: Of those patients not at NCEP ATP III LDL goal with simvastatin monotherapy, 73% reached their LDL goal following the switch to another statin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin, after simvastatin therapy vs lovastatin, after simvastatin monotherapy vs pravastatin, after simvastatin monotherapy vs fluvastatin, after simvastatin monotherapy vs simvastatin-ezetimibe, after simvastatin monotherapy	switched to other statin therapy		Secondary: Not reported	
Fox et al.[109] (2007) Rosuvastatin (average dose, 11.7 mg/day) vs	RETRO Adult patients with diabetes who were newly prescribed a statin between August 2003 and March 2006	N=4,754 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction from baseline in LDL-C, proportion of patients achieving LDL-C goal <100	Primary: Rosuvastatin was associated with a significant reduction in small dense LDL-C compared to atorvastatin (22.5%), simvastatin (20.1%), pravastatin (13.7%), lovastatin (17.3%) and fluvastatin (15.8%) (P<0.0001 for all). Compared to other statins, a significantly greater proportion of patients receiving rosuvastatin achieved the LDL-C goal (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
other statins (atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin; dosed 17 to 64 mg/day)			mg/dL Secondary: Not reported	Not reported
Ballantyne et al.[110] (2007) EXPLORER Ezetimibe 10 mg QD and rosuvastatin 40 mg QD vs rosuvastatin 40 mg QD	MC, OL, PG, RCT Men and women aged ≥18 years with hypercholesterolemia, history of CHD or clinical evidence of atherosclerosis or CHD risk equivalent (10-year CHD risk score >20%), 2 most recent fasting LDL-C levels of ≥160 mg/dL and <250 mg/dL	N=469 6 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal (<100 mg/dL) after 6 weeks of treatment Secondary: Percentage of patients achieving the ATP III non-HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL, percentage of patients achieving the 2003 European LDL goal of <100 or 115 mg/dL and	Primary: Significantly more patients in the combination therapy group achieved the LDL-C goal of <100 mg/dL at week six compared to rosuvastatin alone (94 vs 79.1%; P<0.001). Secondary: The non-HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL were achieved by a significantly higher percentage of patients in the combination therapy group than the monotherapy group (88 patients or 37.4% and 80 patients or 34.8%, respectively; P<0.001). There was a significantly higher percent of patients in the combination therapy group achieving the European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals (LDL <100 or 115 mg/dL and TC <175 or 190 mg/dL), depending on risk category compared to the rosuvastatin group alone at week six (LDL 93.6 vs 74.3%, LDL and TC 90.6 vs 68.3%, respectively; P<0.001). At week six, the combination therapy group had a significantly greater percent reduction of 69.8% in the LDL level compared to a 57.1% reduction in the monotherapy group (P<0.001). Significantly greater reductions in TC, non-HDL-C and TG levels were seen in the combination group compared to the monotherapy group (P<0.001). Both treatment groups increased HDL level to a similar extent (P=0.151). LDL:HDL, TC:HDL and non-HDL:HDL cholesterol ratios decreased significantly more in patients receiving combination therapy compared to patients receiving monotherapy (all P<0.001). Significant decreases in apo B and the apo B:apo AI ratio were seen in the combination therapy group compared to the monotherapy group (P<0.001 for both). Apo AI increased by 3.2% and 1.6% in the combination therapy and monotherapy groups, respectively (P=0.202). The median percent

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			combined LDL and TC goals of <100 or 115 mg/dL and <175 or 190 mg/dL, respectively, depending on risk category, percentage change from baseline in LDL, HDL, TC, TG, non-HDL, lipid ratios (LDL:HDL, TC:HDL and non-HDL:HDL), apo AI, apo B, and apo B:apo AI ratio, and changes in hsCRP in at week six, safety and tolerability	decrease in CRP was significantly higher with combination therapy than monotherapy (-46.4 vs -28.6%; P<0.001). The overall frequency and type of adverse events were similar in both groups, with 31.5% of patients on combination therapy and 33.5% of patients on monotherapy reporting any adverse event. No adverse events were considered related to ezetimibe; the most frequently reported adverse event was myalgia (3.0% of patients in the rosuvastatin-alone group and 2.9% in the rosuvastatin plus ezetimibe group). There were two patients (0.8%) in the combination therapy group and three patients (1.3%) in the monotherapy group who discontinued the study due to treatment-related adverse events. One death occurred in the combination therapy group due to acute myocardial infarction and this was not considered to be related to study treatment. ALT increases >3 times the upper limit of normal were recorded in three patients, all in the combination therapy group.
Hong et al.[111] (2018) I-ROSETTE Ezetimibe 10 mg/rosuvastatin 20 mg vs	DB, MC, RCT Patients 19 to 79 years of age with hypercholesterolemia requiring medical treatment	N=389 8 weeks	Primary: Change from baseline in LDL-C between the ezetimibe/rosuvastatin and rosuvastatin treatment groups	Primary: The percent changes in adjusted mean LDL-C level at eight weeks compared with baseline values were –57.0% and –44.4% in the total ezetimibe/rosuvastatin and total rosuvastatin groups, respectively. Treatment with ezetimibe/rosuvastatin resulted in a greater lipid-lowering effect compared with treatment with rosuvastatin alone (differences, –12.6 mg/dL; 95% CI, –16.5 to –8.6; P<0.001). Secondary: The most common adverse events were gastrointestinal disorders, followed by

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ezetimibe 10 mg/rosuvastatin 10 mg vs ezetimibe 10 mg/rosuvastatin 5 mg vs rosuvastatin 20 mg vs rosuvastatin 10 mg vs rosuvastatin 5 mg			Secondary: Adverse events	investigations and musculoskeletal and connective tissue disorders. There were no significant differences in the overall incidence of adverse events, adverse drug reactions, or serious adverse events. Laboratory findings, including liver function test results and creatinine kinase levels, were comparable between groups.
Jones et al.[112] (2009) Fenofibric acid 135 mg QD and rosuvastatin (10 or 20 mg) QD vs fenofibric acid 135 mg QD	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=1,445 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-	Primary: Combination therapy (rosuvastatin 10 and 20 mg) was associated with a significantly greater increase in HDL-C (10 mg: 20.3 vs 8.5%; P<0.001 and 20 mg: 19.0 vs 10.3%; P<0.001) and a significantly greater decrease in TG (10 mg: 47.1 vs 24.4%; P<0.001 and 20 mg: 42.9 vs 25.6%; P<0.001) compared to rosuvastatin (10 and 20 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (10 mg: 37.2 vs 6.5%; P<0.001 and 20 mg: 38.8 vs 6.5%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (rosuvastatin 10 mg) was associated with a significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs rosuvastatin 10, 20, or 40 mg QD			HDL-C, VLDL-C, TC, apo B and hsCRP	greater reduction in non-HDL-C compared to fenofibric acid or rosuvastatin (10 mg) (P<0.001). Combination therapy was also associated with significantly greater improvements in VLDL-C (P<0.001), apo B (P<0.001) and hsCRP (P=0.013) compared to rosuvastatin. Combination therapy (rosuvastatin 20 mg) significantly improved non-HDL-C compared to fenofibric acid (P<0.001) and was associated with a significantly greater improvement in VLDL-C (P=0.038) and hsCRP (P=0.010) compared to rosuvastatin (20 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
Roth et al.[113] (2010) Rosuvastatin 5 mg/day vs fenofibric acid 135 mg/day vs rosuvastatin 5 mg/day plus fenofibric acid 135 mg/day	DB, MC, RCT Patients with fasting LDL-C ≥130 mg/dL, TG ≥150 mg/dL and HDL-C 40 mg/dL	N=760 12 weeks (plus a 30 day safety follow up period)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Changes from baseline in non-HDL-C, VLDL-C, apo B, hsCRP and TC; safety; proportion of patients achieving LDL-C (<100 mg/dL) and non-HDL-C (<130 mg/dL) goals	Primary: Combination therapy resulted in a significantly greater mean percent change in HDL-C (23.0 vs 12.4%; *P*<0.001) and TG (-43.0 vs -17.5%; *P*<0.001) compared to rosuvastatin, and resulted in significantly higher mean percent decrease in LDL-C compared to fenofibric acid (28.7 vs 4.1%; *P*<0.001). Secondary: Combination therapy resulted in significantly greater improvements in non-HDL-C compared to either monotherapy, and significantly greater improvements in apo B, hsCRP, VLDL-C and TC compared to rosuvastatin. All treatments were generally well tolerated, with discontinuations due to adverse events being higher with combination therapy (8.3%) and fenofibric acid (7.5%) compared to rosuvastatin (4.4%). The most common adverse events leading to discontinuation were myalgia and muscle spasms and nausea, fatigue and ALT and AST increases. The overall incidence of treatment-emergent adverse events was similar across treatments (58.5 to 63.0%). No significant differences were observed between the combination therapy and either monotherapy in the incidence of any category of adverse events (muscle, hepatic and renal related). In patients with a 10 year CHD risk >20%, the LDL-C goal <100 mg/dL was achieved by 50.5% of patients receiving combination therapy and rosuvastatin; the non-HDL-C goal <130 mg/dL was achieved by 49.5% of patients receiving combination therapy compared to 33.3% of patients receiving rosuvastatin (*P*=0.03). Both LDL-C and non-HDL-C goals were achieved by 44.3 vs 32.3% (*P*=0.10).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Ferdinand et al.[114] (2012) Fenofibric acid 135 mg QD and rosuvastatin 10 mg QD for 12 weeks, followed by fenofibric acid 135 mg QD and rosuvastatin 20 mg QD for up to 52 weeks Outcomes were evaluated from the end of the initial 12 week period (baseline) up to 52 weeks of treatment.	Post-hoc analysis Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=187 1 year	Primary: Change in baseline LDL-C, HDL-C, non-HDL-C, apo B, TG, hsCRP; proportion of patients achieving individual and combined goals for LDL-C and non-HDL-C; safety Secondary: Not reported	Primary: Increasing rosuvastatin from 10 to 20 mg, in combination with fenofibric acid for up to 52 weeks, resulted in significant changes from baseline in LDL-C (-9.5%), non-HDL-C (-0.6%), apoB (-8.5%), and HDL-C (3.6%) (P≤0.005 for all). TG levels remained unchanged (0.8%; P=0.055) at week 52. A greater proportion of patients achieved risk-stratified lipid goals at week 52 compared to baseline for LDL-C (89 vs 84%; P=0.26), non-HDL-C (50 vs 25%; P value not reported), and both LDL-C and non-HDL-C (50 vs 19%; P value not reported). The incidences of muscle-, hepatic-, and renal-related adverse events and laboratory values were within the expected range for combination therapy. The most commonly reported treatment-emergent adverse events (>10%) were upper respiratory tract infection (14.4%), headache (13.9%), and back pain (10.7%)/ Treatment-emergent serious adverse events occurred in seven percent of patients, and one death (MI) occurred, none of which were deemed to be treatment-related. Secondary: Not reported
Mohiuddin et al.[115] (2009) Fenofibric acid 135 mg QD plus simvastatin 20 to 40 mg QD vs fenofibric acid 135 mg QD vs	AC, DB, MC Patients >18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, and LDL-C ≥130 mg/dL)	N=657 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC,	Primary: Combination therapy was associated with a significantly greater increase in HDL-C (20 mg: 17.8 vs 7.2%; P<0.001 and 40 mg: 18.9 vs 8.5%; P<0.001) and a significantly greater decrease in TG (20 mg: 37.4 vs 14.2%; P<0.001 and 40 mg: 42.7 vs 22.4%; P<0.001) compared to simvastatin (20 and 40 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (20 mg: 24.0 vs 4.0%; P<0.001 and 40 mg: 25.3 vs 4.0%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (simvastatin 20 mg) was associated with a significantly greater decrease in non-HDL-C (P<0.001) compared to fenofibric acid and simvastatin (20 mg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 20 to 80 mg QD			apo B and hsCRP	Combination therapy (simvastatin 20 mg) was associated with significant improvements in VLDL-C (P<0.001), apo B (P<0.001) and hsCRP (P=0.013) compared to simvastatin (20 mg). Combination therapy (simvastatin 40 mg) significantly (P<0.001) improved non-HDL-C compared to fenofibric acid, and resulted in a significantly greater improvement in VLDL-C (P=0.005) compared to simvastatin (40 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
May et al.[116] (2008) DIACOR Fenofibrate 160 mg and simvastatin 20 mg QD vs fenofibrate 160 mg QD vs simvastatin 20 mg QD	DB, PC, RCT Patients with type 2 diabetes, no CHD, and biochemical evidence of mixed dyslipidemia (having 2 of the following 3 lipid parameters: LDL-C >100 mg/dL, TG >200 mg/dL, and HDL-C <40 mg/dL)	N=300 12 weeks	Primary: Lipid and lipoprotein profiles Secondary: Not reported	Primary: Fenofibrate plus simvastatin significantly reduced dense VLDL-C compared to fenofibrate (P<0.001) and simvastatin (P<0.0001). Simvastatin significantly reduced IDL-C compared to fenofibrate (P<0.003). The percentage of LDL-C pattern B constituting total LDL-C was significantly reduced by fenofibrate (-13.7%, P<0.0001) and fenofibrate plus simvastatin (-11.1%, P<0.0001). There was no significant change with simvastatin (-2.4%, P=0.27). Fenofibrate and fenofibrate plus simvastatin significantly increased the percentage of buoyant LDL-C constituting total LDL-C (-19.6%, P<0.0001 and -16.9%, P<0.0001, respectively). There was no significant change with simvastatin (-3.1%, P=0.06). Secondary: Not reported
Derosa et al.[117] (2009) Fenofibrate 145 mg/day and simvastatin 40 mg/day vs fenofibrate 145	RCT, DB, MC Caucasian patients ≥18 years of age with type 2 diabetes mellitus and combined dyslipidemia who had never been treated with lipid-lowering	N=241 12 months	Primary: Lipid and lipoprotein profiles at six and 12 months Secondary: Not reported	Primary: After six months of therapy, there was a significant reduction in TC and LDL-C with simvastatin and fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively). There was no significant change in the fenofibrate group. After 12 months of therapy, there was a significant decrease in TC and LDL-C in all treatment groups (P<0.05 for fenofibrate, P<0.01 for the simvastatin and P<0.001 for fenofibrate plus simvastatin). TC was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). LDL-C was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day vs simvastatin 40 mg/day	medications			After six months of therapy, there was a significant reduction in TG with fenofibrate and fenofibrate plus simvastatin (P<0.05, respectively). There was no significant change in the simvastatin group. After 12 months of therapy, there was a significant decrease in TG in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate plus simvastatin). TG was significantly lower with fenofibrate + simvastatin compared to fenofibrate (P<0.05) or simvastatin (P<0.01). After six months of therapy, there was a significant increase in HDL-C with fenofibrate and fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively). There was no change in the simvastatin group. After 12 months of therapy, there was a significant increase in HDL-C in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate plus simvastatin). HDL-C was significantly higher with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). After six months of therapy, there was no significant change in apo A1 or apo B in any treatment group. After 12 months of therapy, there was a significant increase of apo A1 with fenofibrate plus simvastatin. There was no significant difference between the treatment groups. After 12 months of therapy, there was a significant decrease of apo B in all groups (P<0.05 for fenofibrate, P<0.05 for simvastatin and P<0.01 for fenofibrate plus simvastatin). There was no significant difference between the treatment groups. There were no significant differences in Lp(a) after six or 12 months of therapy in any of the treatment groups. After six months of therapy, there was a significant decrease in hsCRP with fenofibrate plus simvastatin (P<0.05), but not in the other groups. After 12 months of therapy, there was a significant decrease in hsCRP with simvastatin and with fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively), but not with fenofibrate. The hsCRP value was significantly lower with fenofibrate plus simvastatin compared to fenofibrate or simvastatin (P<0.05). Secondary: Not reported
Rogers et al.[118]	MA (18 trials)	N=8,320	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2007) Simvastatin 10, 20, 40 or 80 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day	Patients >18 years of age with elevated TC and LDL-C	Up to 12 weeks	Reductions in TC, LDL-C and TG; increases in HDL-C Secondary: Not reported	Simvastatin appeared to be comparable to atorvastatin in terms of TC reduction from baseline at four times the dose of atorvastatin (P>0.05). Simvastatin 20 and 40 mg were less effective at reducing LDL-C from baseline compared to atorvastatin 40 and 80 mg, respectively (P<0.001). Simvastatin 40 to 80 mg was comparable to atorvastatin 20 mg in terms of TG reduction from baseline (P=0.22 and P=0.53, respectively). Atorvastatin 40 to 80 mg was more effective in reducing TG from baseline compared to all simvastatin doses evaluated (P<0.001). Simvastatin 10, 20 and 80 mg were more effective than atorvastatin 80 mg in increasing HDL-C from baseline (P<0.05). Secondary: Not reported
Hall et al.[119] (abstract) (2009) SPACE ROCKET Simvastatin 40 mg/day vs rosuvastatin 10 mg/day	MC, OL, RCT Patients with a history of acute MI	N=1,263 3 months	Primary: Proportion of patients achieving the European Society of Cardiology 2003 TC (<174 mg/dL) or LDL-C (<97 mg/dL) goals Secondary: Not reported	Primary: There was no difference between the two treatments in the proportions of patients who achieved lipid goals (77.6 vs 79.9%; OR, 1.16; 95% CI, 0.88 to 1.53; P=0.29). A post hoc analysis demonstrated a significantly higher achievement of the new European Society of Cardiology, American Heart Association and American College of Cardiology LDL-C goal (<70 mg/dL) with rosuvastatin (37.8 vs 45.0%; OR, 1.37; 95% CI, 1.09 to 1.72; P=0.007). The proportion of patients achieving the Fourth Joint Task Force European Guidelines TC (<155 mg/dL) and LDL-C (<77 mg/dL) goals were also significantly higher with rosuvastatin (38.7 vs 47.7%; OR, 1.48; 95% CI, 1.18 to 1.86; P=0.001). Secondary: Not reported
Feldman et al.[120] (2004) Ezetimibe 10 mg/day plus	DB, MC, RCT Patients 18 to 80 years of age with CHD or CHD risk	N=710 23 weeks	Primary: Proportion of patients with LDL-C <100 mg/dL at week	Primary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week five compared to patients receiving simvastatin (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 10, 20 or 40 mg/day vs simvastatin 20 mg/day	equivalent disease and LDL-C ≥130 mg/dL and TG ≤350 mg/dL		five Secondary: Proportion of patients with LDL-C <100 mg/dL at 23 weeks	Secondary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week 23 compared to patients receiving simvastatin (P<0.001). At five weeks, there was a significant reduction in TC, non-HDL-C, apo B, TC:HDL-C and LDL-C:HDL-C with combination therapy compared to simvastatin (P<0.001 for all). HDL-C was significantly increased with combination therapy (10/20 mg) compared to simvastatin (P<0.05). At five weeks, combination therapy was associated with a significant reduction in TG compared to simvastatin (P<0.05). Treatment-related adverse effects were similar with simvastatin and combination therapy (10/10, 10/20 and 10/40 mg) (7.5, 9.6, 14.0 and 10.0%, respectively; P values not reported).
Gaudiani et al.[121] (2005) Ezetimibe 10 mg/day plus simvastatin 20 mg/day vs simvastatin 40 mg/day All patients received simvastatin 20 mg/day for a 6 week run in period.	DB, MC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes (HbA_{1c} ≤9.0%), treated with a stable dose of pioglitazone (15 to 45 mg/day) or rosiglitazone (2 to 8 mg/day) for ≥3 months, LDL-C >100 mg/dL and TG <600 mg/dL (if already on a statin therapy)	N=214 30 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and apo AI	Primary: LDL-C was reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin (20.8 vs 0.3%; P<0.001). Secondary: TC (14.5 vs 1.5%; P<0.001), non-HDL-C (20.0 vs 1.7%; P<0.001), apo B (14.1 vs 1.8%; P<0.001), LDL-C:HDL-C (P<0.001), TC:HDL-C (P<0.001) and apo AI (P<0.001) were reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin. The increase in HDL-C was similar between the two treatments (P value not reported). The incidence of treatment-related adverse effects was lower with simvastatin compared to combination therapy (10.0 vs 18.3%, respectively; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Bays et al.[122] (2008) Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day	ES Patients ≥18 years of age with primary hypercholesterolemia	N=768 48 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: In general, combination therapy did not substantively differ from simvastatin with respect to total adverse events (73 vs 69%), treatment related adverse events (13.5 vs 11.4%), treatment related serious adverse events (1 vs 0%), discontinuations due to treatment related adverse events (2.8 vs 2.6%) or discontinuations due to treatment-related serious adverse events (1 vs 0%). Combination therapy had a slightly higher rate of serious adverse events (5.2 vs 2.6%) and discontinuations due to adverse events (4.5 vs 2.6%) compared to simvastatin (P>0.20). Based on investigator assessment of causality, rates were similar between the treatments. There are no remarkable observations of between-treatment group differences whether or not they are related to a specific tissue or body system. In general, combination therapy did not differ from simvastatin with respect to total laboratory adverse events (12 vs 12%), treatment related laboratory adverse events (6.2 vs 5.3%), total laboratory serious adverse events (0 vs 0%), treatment related laboratory serious adverse events (0 vs 0%) or discontinuations due to laboratory serious adverse events (0 vs 0%). Secondary: Not reported
Calza et al.[123] (abstract) (2008) Rosuvastatin 10 mg QD vs pravastatin 20 mg QD vs	OL, PRO, RCT Patients with HIV receiving protease inhibitor therapy ≥12 months with protease inhibitor-associated hypercholesterolemia ≥3 months and unresponsive to a hypolipidemic diet and physical	N=94 12 months	Primary: Changes from baseline in TC and LDL-C Secondary: Not reported	Primary: Statins led to a mean reduction of 21.2 and 23.6% in TC and LDL-C (P=0.002). The mean decrease in TC was significantly greater with rosuvastatin (25.2%) compared to pravastatin (17.6%; P=0.01) and atorvastatin (19.8%; P=0.03). During the 12 months, all statins demonstrated a favorable tolerability profile, and patient's HIV viral load did not present any variation. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 10 mg QD	exercise			
Faergeman et al.[124] (2008) ECLIPSE Rosuvastatin 10 mg for 6 weeks; dose was force-titrated every 6 weeks to maximal dose (40 mg) vs atorvastatin 10 mg for 6 weeks; dose was force-titrated every 6 weeks to maximal dose (80 mg) Doses could be decreased for safety reasons.	RCT, OL, MC, PG Patients ≥18 years of age with hypercholesterolemia and a history of CHD, clinical evidence of atherosclerosis or a 10-year CHD risk score >20% (CHD risk equivalent)	N=1,036 24 weeks	Primary: Percentage of patients achieving NCEP ATP III LDL-C goal <100 mg/dL after 24 weeks Secondary: Percentage of patients achieving NCEP ATP III LDL-C goal <100 mg/dL at weeks 6, 12 and 18; achievement of the following NCEP ATP III goals at all time points: non-HDL-C <130 mg/dL, 2003 European LDL-C goals (100-115 mg/dL and combined LDL-C and TC goals (LDL-C 100-115 mg/dL	Primary: A greater percentage of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin than with atorvastatin at week 24 (83.6 vs 74.6%; P<0.001). Secondary: A greater percentage of patients achieved the NCEP ATP III non-HDL-C goal with rosuvastatin than with atorvastatin (week 6, 41.9 vs 19.6%; week 12, 64.5 vs 32.0%; week 18, 76.0 vs 55.0%; week 24, 79.6 vs 68.0%; P<0.02 at each time point). A greater percentage of patients achieved the 2003 European LDL-C goals and the combined LDL-C and TC goals with rosuvastatin than with atorvastatin at all time points (P<0.001). Significantly greater reductions in LDL-C, TC and non-HDL-C levels, and increases in HDL-C were achieved with rosuvastatin than with atorvastatin at all time points. The reductions in TG levels were similar in both treatment groups at all time points except at week 24, when a significantly greater decrease was observed in patients receiving atorvastatin compared to those receiving rosuvastatin (P<0.05). Significantly greater mean reductions in LDL-C:HDL-C, TC:HDL-C, non-HDL-C:HDL-C and apoB:apo AI ratios were achieved with rosuvastatin than with atorvastatin at all time points (P<0.001). Adverse events were experienced by 53.7 and 52.5% of patients receiving rosuvastatin and atorvastatin, respectively. Myalgia was the most frequently reported adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			and TC 175 or 190 mg/dL), percentage changes from baseline in LDL-C, HDL-C, TC, TG, non-HDL-C, and lipid ratios	
Insull et al.[125] (2007) SOLAR Rosuvastatin 10 mg/day daily for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs atorvastatin 10 mg/day for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved	MC, RCT Patients ≥18 years of age who were enrolled in a managed care health plan and classified as high risk by NCEP ATP III risk assessment	N=1,632 12 weeks	Primary: Proportion of patients achieving NCEP ATP III high risk LDL-C goal (<100 mg/dL) at week six Secondary: Proportion of patients achieving the high risk LDL-C goal at 12 weeks, proportion of hyper-triglyceridemic patients who achieved both the LDL-C goal (<100 mg/dL) and the non-HDL-C goal (<130 mg/dL) for high risk	Primary: After six weeks, a significantly greater proportion of patients receiving rosuvastatin 10 mg achieved the high risk LDL-C goal compared to patients receiving atorvastatin 10 mg and patients receiving simvastatin 20 mg (65 vs 41 vs 39%, respectively; P<0.001). Secondary: After 12 weeks, 76% of patients receiving rosuvastatin 20 mg achieved the high risk LDL-C goal compared to 58 and 53% of patients receiving atorvastatin 20 mg and simvastatin 40 mg, respectively (P<0.001). After six weeks, 44% of hypertriglyceridemic patients receiving rosuvastatin 10 mg achieved the combined LDL-C and non-HDL-C goals compared to 19% of patients receiving simvastatin 20 mg, respectively (P<0.001). There was no difference between rosuvastatin 10 mg and atorvastatin 10 mg (44 vs 22%; P value not reported). After 12 weeks, 57% of hypertriglyceridemic patients taking rosuvastatin 20 mg reached the combined LDL-C and non-HDL-C goal compared to 31% of patients taking simvastatin 40 mg, respectively (P<0.001). There was no difference between rosuvastatin 20 mg and atorvastatin 20 mg (57 vs 36%; P value not reported). Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin and simvastatin at six and 12 weeks (P<0.001 for both). Rosuvastatin was associated with a significant reduction in TC compared to atorvastatin and simvastatin at six and 12 weeks (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs simvastatin 20 mg/day for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved All patients were randomized after a 6 week dietary lead in period.			patients, changes from baseline in LDL-C and other lipid parameters at six and 12 weeks	Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin and simvastatin at six and 12 weeks (P<0.001). Rosuvastatin was associated with a significant reduction in non-HDL-C:HDL-C compared to atorvastatin and simvastatin at six and 12 weeks (P<0.001). Rosuvastatin was associated with a significant increase in HDL-C compared to atorvastatin and simvastatin at 12 weeks (P<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TG from baseline compared to simvastatin at six and 12 months (P<0.001). The frequency and types of adverse events were similar with all treatments (P value not reported).
Ballantyne et al.[126] (2006) MERCURY II Rosuvastatin 20 mg/day for 8 weeks vs atorvastatin 10 or 20 mg/day for 8 weeks vs simvastatin 20 or 40 mg/day for 8	MC, OL, RCT Patients ≥18 years of age, at high risk for CHD events, fasting LDL-C ≥130 to <250 mg/dL on 2 separate measurements within 15% of each other and a fasting TG <400 mg/dL	N=1,993 16 weeks	Primary: The proportion of patients achieving LDL-C <100 mg/dL at week 16 Secondary: The proportion of patients meeting the LDL-C target at week eight, change in lipid and lipoprotein measures at weeks eight and 16, adverse events	Primary: After 16 weeks, a larger proportion of patients receiving rosuvastatin achieved the LDL-C goal compared to patients receiving all other treatments (83, 42, 64, 32 and 56%, respectively; P value not reported). After 16 weeks, significantly more patients who switched to rosuvastatin therapy achieved LDL-C target level <100 mg/dL compared to patients who remained on their initial statin therapy (P<0.001). Secondary: After 16 weeks, patients who switched to rosuvastatin experienced a significant LDL-C reduction from baseline compared to patients remaining on their initial medication regimen (P<0.001). After eight weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the LDL-C goal <100 mg/dL compared to patients receiving all other treatments (82, 43, 62, 33 and 55%, respectively; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
weeks All patients were randomized after a 6 week dietary lead in period. After 8 weeks of treatment, patients received an additional 8 weeks of either initial statin or rosuvastatin therapy.				After 16 weeks, a significantly greater proportion of patients randomized to rosuvastatin achieved the LDL-C goal <70 mg/dL compared to patients receiving all other treatments (37, 7, 13, 1 and 10%, respectively; P value not reported). After 16 weeks, patients who switched to rosuvastatin experienced a significant atherogenic lipid measure and ratio reduction from baseline compared to patients remaining on their initial medication regimen (P<0.001). After 16 weeks, a significantly greater proportion of hypertriglyceridemic patients receiving rosuvastatin achieved the LDL-C goal <100 mg/dL and non-HDL-C goals compared to patients receiving all other treatments (80, 20, 42, 19 and 29%, respectively; P value not reported). The frequency and type of adverse events were similar with all treatments (P value not reported). In addition, there were no symptomatic adverse events associated with hepatic dysfunction.
Jones et al.[127] (2003) STELLAR Rosuvastatin 10 to 40 mg/day vs pravastatin 10 to 40 mg/day vs atorvastatin 10 to 80 mg/day vs simvastatin 10 to	OL, PG Patients ≥18 years of age with hypercholesterolemia and LDL-C ≥160 to <250 mg/dL at the 2 most recent consecutive visits	N=2,431 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent changes from baseline in HDL-C, TG and TC	Primary: Compared to all doses of atorvastatin and pravastatin, rosuvastatin was associated with a greater reduction in LDL-C (P<0.001 for both). When compared to baseline, the following reductions in LDL-C were observed: rosuvastatin; 45.8 to 55.0%, atorvastatin; 36.8 to 51.1%, simvastatin; 28.3 to 45.8% and pravastatin; 20.1 to 29.7%. The greatest reductions in LDL-C observed were a 55% reduction with rosuvastatin 40 mg and a 51% reduction with atorvastatin 80 mg (P=0.006). Secondary: Rosuvastatin 10 to 40 mg/day was associated with a 7.7 to 9.6% increase in HDL-C, a 19.8 to 26.1% reduction in TG and a 32.9 to 40.2% reduction in TC (P values not reported). Pravastatin 10 to 40 mg/day was associated with a 3.2 to 5.6% increase in HDL-C, a 7.7 to 13.2% reduction in TG and a 14.7 to 21.5% reduction in TC (P value not reported). Atorvastatin 10 to 80 mg/day was associated with a 2.1 to 5.7% increase in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
80 mg/day				HDL-C, a 20.0 to 28.2% reduction in TG and a 27.1 to 38.9% reduction in TC (P value not reported). Simvastatin 10 to 80 mg/day was associated with a 5.2 to 6.8% increase in HDL-C, an 11.9 to 18.2% reduction in TG and a 20.3 to 32.9% reduction in TC (P value not reported).
Welty et al.[128] (2016) STELLAR Rosuvastatin 10 to 40 mg/day vs pravastatin 10 to 40 mg/day vs atorvastatin 10 to 80 mg/day vs simvastatin 10 to 80 mg/day	Subgroup analysis Women in the STELLAR trial with LDL-C ≥160 and <250 mg/dL and triglycerides <400 mg/dL	N=1,146 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent changes from baseline in HDL-C, TG and TC	Primary: Statin treatment produced dose-related decreases in LDL-C levels ranging from 21 to 57% at six weeks, depending on the statin and dose used. At the lowest statin dose, 10 mg, LDL-C was reduced by 49% with rosuvastatin, 39% with atorvastatin, 30% with simvastatin, and 21% with pravastatin (P<0.002 rosuvastatin vs all comparators). A similar pattern was observed for the high-intensity doses of statins defined by the ACC/AHA guideline and recommended for those at risk of atherosclerotic cardiovascular disease: LDL-C reductions were 53% with rosuvastatin 20 mg, 57% with rosuvastatin 40 mg, 47% with atorvastatin 40 mg, and 51% with atorvastatin 80 mg. Rosuvastatin 20 mg produced statistically greater reductions in LDL-C compared with atorvastatin 20 mg and 40 mg (P<0.002 for both comparisons). In addition, rosuvastatin 40 mg produced statistically greater reductions in LDL-C compared with atorvastatin 40 mg (P<0.002). Secondary: Reductions in non-HDL-C levels ranged from 45% to 53% with rosuvastatin, 37% to 48% with atorvastatin, 27% to 44% with simvastatin, and 19% to 28% with pravastatin. Reductions in non-HDL-C with rosuvastatin 10 mg were significantly greater when compared with atorvastatin 10 mg; simvastatin 10, 20, or 40 mg; and pravastatin 10, 20, or 40 mg (P<0.002 for all comparisons). Rosuvastatin 20 mg reduced non-HDL-C significantly more than milligram-equivalent doses of atorvastatin, simvastatin, and pravastatin (P<0.002 for all comparisons). The increases in HDL-C were numerically greater with rosuvastatin than with the other statins, but the differences were not statistically significant, except that rosuvastatin 20 and 40 mg increased HDL-C significantly more than milligram-equivalent or higher doses of atorvastatin. All statins reduced triglyceride levels, with similar effects across the dose

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				range for rosuvastatin and atorvastatin, and a trend for dose-related reductions for simvastatin and pravastatin.
McKenney et al.[129] (2007) COMPELL Rosuvastatin 10 mg/day for 4 weeks, followed by 20 mg/day for 4 weeks, followed by 40 mg/day vs atorvastatin 20 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by atorvastatin 20 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day vs simvastatin 20 mg/day plus ezetimibe 10	MC, OL, PG, RCT Patients ≥21 years of age with hyper-cholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL	N=292 12 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects	Primary: Atorvastatin plus niacin SR, rosuvastatin plus niacin SR, simvastatin plus ezetimibe and rosuvastatin were associated with similar reductions in LDL-C (56, 51, 57 and 53%, respectively; P=0.093). Secondary: Atorvastatin plus niacin SR was associated with a significant increase in HDL-C compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (22, 10 and 7%, respectively; P≤0.05). There was no significant differences in the reduction of non-HDL-C from baseline with any treatment (P=0.053). Atorvastatin plus niacin SR was associated with a significant reduction in TG compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (47, 33 and 25%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in Lp(a) compared to simvastatin plus ezetimibe and rosuvastatin (20 mg)-containing therapy (-14, 7 and 18%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in apo B compared to rosuvastatin (43 vs 39%, respectively; P≤0.05). Side effects were similar across treatments (P values not reported). There were no cases of myopathy or hepatotoxicity reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10 mg/day vs rosuvastatin 10 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by rosuvastatin 10 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by rosuvastatin 20 mg/day plus niacin SR 1,000 mg/day				
Bays et al.[130] (2008) Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) Extension study	MC, OL Patients with mixed dyslipidemia completing 1 of 3 MC, PRO, DB, RCT 12-week studies were eligible	N=2,201 1 year	Primary: Safety, percent changes from baseline in TG, HDL-C, and LDL-C Secondary: Percent changes in non-HDL-C, VLDL-C, TC, apoB, and hsCRP	Primary: Of the 2,201 patients who received at least one dose of fenofibric acid plus statin combination therapy, six patients (0.3%) died during the conduct of the ES; no death was considered by the investigator to be treatment related. Overall, 148 (6.7%) patients had treatment-emergent serious adverse events (fenofibric acid plus rosuvastatin, 7.2%; fenofibric acid plus simvastatin, 7.8%; fenofibric acid plus atorvastatin 4.6%). The most common treatment-emergent serious adverse events were osteoarthritis, deep vein thrombosis, coronary artery disease, MI, and chest pain, diverticulitis, syncope, and intervertebral disc protrusion. A total of 1,856 patients (84.3%) had one or more treatment-emergent adverse events (fenofibric acid plus rosuvastatin, 83.1%; fenofibric acid plus

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
patients received the same type of statin that was used in the statin-containing arms of the controlled study in which they participated.				simvastatin, 86.2%; fenofibric acid plus atorvastatin, 85.2%). The most frequently reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, and back pain. Among patients who received fenofibric acid monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-22.0%), mean percent decrease in LDL-C (-38.1%), and mean percent increase in HDL-C (6.2%). Among patients who received moderate-dose statin monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-30.5%) and mean percent increases in HDL-C (13.1%) and LDL-C (3.1%). Among patients who received fenofibric acid plus low-dose statin combination therapy in a controlled study, there was an additional median percent decrease in TG (-4.2%), mean percent increase in HDL-C (4.8%), and mean percent decrease in LDL-C (-9.7%) after the statin dose was increased for 52 weeks. The group of patients who were treated with fenofibric acid plus moderate-dose statin in a controlled study and continued the same therapy in the extension study exhibited sustained improvements in lipid parameters throughout the course of therapy. For this group of patients, treatment with fenofibric acid plus moderate-dose statin combination therapy for a total of 64 weeks decreased TG from a mean baseline of 297.8 mg/dL to a mean final level of 138.0 mg/dL, decreased LDL-C from a mean baseline of 153.1 mg/dL to a mean final level of 94.2 mg/dL, and increased HDL-C from a mean baseline of 38.2 mg/dL to a mean final level of 47.7 mg/dL. Secondary: Among patients who received fenofibric acid monotherapy or moderate-dose statin monotherapy in the controlled studies, treatment with fenofibric acid plus moderate-dose statin combination therapy in the extension study resulted in additional mean percent decreases in non-HDL-C, VLDL-C, TC, and apo B, and median percent decrease in hsCRP that were sustained throughout 52

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				weeks of combination therapy. For patients initially treated with fenofibric acid plus low-dose statin combination therapy, increasing the statin dose resulted in additional mean percent decreases in non-HDL-C, TC, and apo B and median percent decrease in hsCRP, which were sustained throughout the study.
Kipnes et al.[131] (2010) Fenofibric acid 135 mg/day plus a moderate dose statin (rosuvastatin 20 mg/day, simvastatin 40 mg/day or atorvastatin 40 mg/day)	ES, OL Patients with mixed dyslipidemia at the start of a 1 year, ES, OL	N=310 1 year (2 years of total therapy)	Primary: Safety and efficacy Secondary: Not reported	Primary: No deaths occurred during the two year trial. The incidence of serious adverse events was numerically highest with fenofibric acid plus rosuvastatin (14.9%) compared to fenofibric acid plus simvastatin (8.0%) or atorvastatin (5.8%). The incidences of adverse events were similar among all treatments as well (94.8, 90.0 and 97.7%). Adverse events tended to occur early in treatment, without the development of new types of adverse events over time. The most common treatment-related adverse events were muscle spasms (3.9%), increased blood creatine phosphokinase (3.5%), headache (2.9%), myalgia (2.9%), dyspepsia (2.3%) and nausea (2.3%). Rhabdomyolysis was not reported with any treatment. Nine patients discontinued therapy due to adverse events, with similar incidences among all treatments. Myalgia was the most common reason for discontinuation. No significant difference in the incidence of laboratory elevations was observed among the treatment groups. Incremental improvements in mean percentage changes in all efficacy variables were observed after the first visit in the year one ES (week 16). This effect was sustained for greater than two years and sizable mean percentage changes in all efficacy variables were observed at week 116. In the overall population, the mean percentage changes from baseline to week 116 in efficacy variables were: 17.4 (HDL-C), -46.4 (TG), -40.4 (LDL-C), -47.3 (non-HDL-C), -37.8 (TC) and -52.8% (VLDL-C). Significant differences among treatments were observed for non-HDL-C (-48.60±13.58 vs -41.70±13.10 vs -47.30±12.50%; P=0.011), TC (-38.70±12.16 vs -32.50±10.86 vs -38.60±10.85%; P=0.007) and VLDL-C (-56.80±25.17 vs -40.30±51.25 vs -51.20±35.42%; P=0.019). Secondary: Not reported
Alrasadi et al.[132] (2008)	XO	N=19	Primary: Percent changes	Primary: <u>Protocol 1</u>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Protocol 1 Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID for 8 weeks Protocol 2 Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on	Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	32 weeks	in HDL-C and TC/HDL-C ratio Secondary: Not reported	The mean percent change in HDL-C was +6, -6, and +22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +19, -26, and -22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). Protocol 2 The mean percent change in HDL-C was -2 and +18% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +32 and -32% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC/HDL-C (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 20 mg throughout the study in Protocol 2.				
Jones et al.[133] (2009) Fenofibric acid 135 mg QD vs low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs fenofibric acid 135 mg plus low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs moderate-dose statin (rosuvastatin 20 mg, simvastatin 40	Pooled analysis of 3 AC, DB, MC, RCT Patients >18 years of age, with HDL-C <40 mg/dL (men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL ≥130 mg/dL	N=2,715 12 weeks	Primary: Mean percent change in HDL-C, TGs (fenofibric acid plus atorvastatin vs atorvastatin), and LDL-C (fenofibric acid plus atorvastatin vs fenofibric acid) Secondary: Mean percent change in non-HDL-C, VLDL-C, TC, apo B, and hsCRP; safety	Primary: Fenofibric acid plus low-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (18.1 vs 7.4%; P<0.001) and a greater mean percent decrease in TG (-43.9 vs -16.8%; P<0.001) compared to low-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-33.1 vs -5.1%; P<0.001) compared to fenofibric acid monotherapy. Fenofibric acid plus moderate-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (17.5 vs 8.7%; P<0.001) and a greater mean percent decrease in TG (-42.0 vs -23.7%; P<0.001) compared to moderate-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-34.6 vs -5.1%; P<0.001) compared to fenofibric acid monotherapy. No formal comparisons were made between the high-dose statin monotherapy group and the other treatment groups. Secondary: Greater improvements in non-HDL-C, VLDL-C, TC, and apo B were observed for fenofibric acid plus low-dose statin combination therapy compared to corresponding monotherapies (P≤0.001). Combination therapy was generally well tolerated, and safety profiles were similar to monotherapies. No rhabdomyolysis was reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg, or atorvastatin 40 mg) QD vs fenofibric acid 135 mg QD plus moderate-dose statin QD vs high-dose statin (rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg) QD				
Bays et al.[134] (2010) COMBOS Omega-3-acid ethyl esters (Lovaza®) 4 g/day plus simvastatin 40 mg/day Patients who received placebo in the COMBOS trial were switched to OL treatment with omega-3-acid	ES, OL of COMBOS Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥8 weeks prior to trial enrollment	N=188 Up to 24 months	Primary: The difference between Nonswitchers and Switchers in median percent change in non-HDL-C from COMBOS end of treatment to month four Secondary: Difference in the median percent change in non-HDL-C	Primary: The percent change in non-HDL-C from COMBOS end of treatment to month four revealed a greater response among Switchers when compared to Nonswitchers. At month four, the median percent change in non-HDL-C from the end of DB treatment was -9.4% in Switchers and 0.9% in Nonswitchers (P<0.001). Secondary: After 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS end of treatment in Nonswitchers vs Switchers was -0.2 vs -0.64% (P=0.027) and 1.6 vs -6.3% (P=0.004). Reductions in non-HDL-C were maintained throughout the trial. After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in the total population was -8.3, -7.3 and -8.9%, respectively (P<0.001 for all). After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in Nonswitchers vs Switchers was -5.4 vs -10.3% (P=0.062), -6.6 vs -8.1%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ethyl esters plus simvastatin (Switchers). Those who received omega-3-acid ethyl esters plus simvastatin in the COMBOS trial were maintained on current therapy (Nonswitchers) All patients continued therapeutic lifestyle changes diet.			from COMBOS end of treatment to month 12 and 24; the change in non-HDL-C from COMBOS baseline to months four, 12 and 24 and from COMBOS end of treatment to months four, 12 and 24; percent changes in TC, HDL-C, LDL-C, VLDL-C, TG and TC:HDL-C for the same time points; HbA_{1c} levels	(P=0.604) and -7.8 vs -9.0% (P=0.496). Consistent with the non-HDL-C response, comparisons of the changes from the COMBOS end of treatment to months four, 12 and 24 in TG and other lipoprotein lipid parameters generally revealed greater reductions in Switchers vs Nonswitchers. The comparisons of the change from COMBOS baseline to these same endpoints reveled generally nonsignificant differences between the two groups. Median percent reductions from COMBOS baseline in TG, TC and VLDL-C in the total population were maintained at months four, 12 and 24 of treatment (P<0.001 for all). Omega-3-acid ethyl esters produced small median percent increases from baseline LDL-C levels at months four, 12 and 24. Among the subset of patients who had HbA_{1c} measured at baseline (n=38), the median absolute change in HbA_{1c} after 24 months of treatment was 0.1% (P value not reported).
Rosen et al.[135] (2013) Ezetimibe/ simvastatin (EZ/S) 10/20 mg vs doubling the run-in statin dose (to simvastatin 40 mg or atorvastatin 20	AC, DB, MC, RCT Patients ≥18 and <80 years old with type 1 or 2 diabetes mellitus (HbA_{1c} ≤ 8.5%) and symptomatic CVD, who were naïve to statin and/or ezetimibe or were taking a stable dose of approved lipid-lowering	N=808 12 weeks (6 weeks of DB treatment after run-in period)	Primary: Percent change from baseline in LDL-C at week 6 Secondary: Percent change from baseline in TC, TG, HDL-C, non-HDL-C, Apo B, Apo A-I, and high-sensitivity C-	Primary: Treatment with EZ/S 10/20 mg resulted in a significantly greater reduction in LDL-C compared with doubling the baseline statin dose (−23.13 vs −8.37%; P< 0.001). In the population of patients receiving simvastatin 20 mg or atorvastatin 10 mg at baseline, the percent reduction in LDL-C was numerically greater when switched to EZ/S than when switched to rosuvastatin 10 mg following six weeks of treatment (−23.13 vs −19.32%; P=0.060). Secondary: There were significantly greater reductions in TC, Apo B, and non-HDL-C in subjects taking EZ/S 10/20 mg compared with subjects who doubled their statin dose and with those taking rosuvastatin 10 mg. For all other lipids and lipoproteins, the percent changes were not statistically significantly different between treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg) vs switching to rosuvastatin 10 mg	therapy		reactive protein (hs-CRP) at week 6 and the percent of patients with LDL-C <70 mg/dL at week 6, safety	The percent of patients reaching LDL-C goal of <70 mg/dL was significantly greater with ezetimibe/simvastatin (54.5%) vs doubling the baseline statin dose (27.0%) or switching to rosuvastatin 10 mg (42.5%). The safety profile appeared generally comparable between all groups.
Bays et al.[136] (2013) PACE Period I: adding ezetimibe 10 mg to stable atorvastatin 10 mg vs doubling atorvastatin to 20 mg vs switching to rosuvastatin 10 mg Subjects in the latter 2 groups who persisted with elevated LDL-C levels (≥100 and ≤160	AC, DB, RCT Patients aged ≥18 and <80 years with primary hypercholesterolemia at high CV risk, lipid-lowering therapy naïve with an LDL-C between 166 and 190 mg/dL, or on a stable dose of statin, ezetimibe, or statin plus ezetimibe having LDL-C-lowering efficacy equivalent to or less than atorvastatin 10 mg After enrollment all patients were administered atorvastatin 10 mg daily as only lipid-lowering therapy for 5 weeks	N=1,547 12 weeks	Primary: Percent change from treated baseline in LDL-C levels at the end of period I Secondary: Percent change from treated baseline in LDL-C at the end of period II; percentage of subjects achieving LDL-C <100 or <70 mg/dl at the end of periods I and II; percent change from treated baseline in other lipids, lipoproteins, and high-sensitivity C-reactive protein	Primary: The addition of ezetimibe to atorvastatin 10 mg produced a greater reduction in LDL-C than doubling the atorvastatin dose to 20 mg or switching to rosuvastatin 10 mg (-22.2, -9.5, and -13.0, respectively; P<0.001, both groups). Secondary: The addition of ezetimibe to atorvastatin 10 mg produced significantly greater attainment of LDL-C <100 or <70 mg/dl and significantly greater reductions in total cholesterol, non–HDL cholesterol, apo B, and LDL-C/HDL-C, total/HDL-C, and non-HDL-C/HDL-C ratios than atorvastatin 20 mg or rosuvastatin 10 mg. The change from baseline in HDL-C, triglycerides, apo AI, and hsCRP were similar among treatments. At the end of period II, ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than atorvastatin 40 mg (17.4 vs 6.9%, P<0.001); switching from rosuvastatin 10 mg to ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than uptitrating to rosuvastatin 20 mg (17.1 vs 7.5%, P<0.001). All treatments were generally well-tolerated.

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mg/dL) after period I, entered period II: subjects on atorvastatin 20 mg had ezetimibe added to their atorvastatin, or uptitrated atorvastatin to 40 mg; subjects on rosuvastatin 10 mg switched to atorvastatin 20 mg plus ezetimibe or uptitrated rosuvastatin to 20 mg			(hsCRP) at the end of periods I and II; assessment of safety and tolerability	
Foody et al.[137] (2013) Add-on group (patients who were initially on simvastatin, atorvastatin, or rosuvastatin monotherapy and added ezetimibe onto this therapy)	OS, RETRO Patients ≥18 years of age with a diagnosis of CHD or CHD risk-equivalent who had a prescription for statin monotherapy with baseline and follow-up LDL-C values, as well as no overlap with other lipid-	N=15,365 Minimum of 6 weeks	Primary: Mean percent change from baseline in LDL-C and percentage of patients attaining LDL-C goals <70 mg/dL and <100 mg/dL Secondary: Not reported	Primary: The mean LDL-C levels at baseline were significantly higher in the add-on groups for each statin compared with those of the titrators. At follow-up, LDL-C levels were reduced more in the add-on groups (80 to 85 mg/dL) than in the titrator groups (87 to 95 mg/dL). Both the absolute changes in LDL-C levels and the percent changes from baseline were significantly greater in the add-on groups than in the titrator groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs titrator group (patients who either titrated their initial statin dose or switched to higher-potency statin monotherapy)	lowering therapy and who had no discontinuations of lipid-lowering therapy at baseline or follow-up during the study period			
Hypertriglyceridemia (Single Entity Agents)				
Hogue et al.[138] (2008) Fenofibrate 200 mg QD vs atorvastatin 20 mg QD	RCT Patients with type 2 diabetes and hypertriglyceridemia	N=40 6 weeks	Primary: Lipids and TRL, inflammation and adhesion molecules Secondary: Not reported	Primary: Treatment with atorvastatin led to a significant decrease in plasma TC (-37.7%; P<0.0001), plasma TG (-37.6%; P<0.0001), plasma apo B (-43.2%; P<.0001), TRL-C (-44.1%; P<0.0001), TRL-TG (-36.9%; P<0.0001), TRL apo B (-13.8%; P=0.04), LDL-C (-43.0%; P<0.0001), LDL apo B (-42.7%; P<0.0001), and a significant increase in HDL-C (17.9%; P=0.001), and HDL apo A-I levels (10.3%; P=0.004). Treatment with fenofibrate led to a significant decrease in plasma C (-10.9%; P=0.0001), plasma TG (-41.4%; P=0.0002), plasma apo B (-9.9%; P=0.01), TRL-C (-52.8%; P<0.0001), TRL-TG (-46.3%; P=0.0002), and TRL apo B (-14.8%; P=0.02) and a significant increase in LDL-C (15.9%; P=0.04) and HDL-C (8.9%; P=0.05). There were significant differences in the percentage changes of plasma cholesterol, plasma apo B, LDL-C, and LDL apo B between the two treatment groups. There was no significant difference in the percentage in changes of plasma TG between the treatment groups. Treatment with atorvastatin significantly decreased plasma levels of CRP (-26.9%; P=0.004), soluble ICAM-1 (-5.4%; P=0.03), soluble VCAM-1 (-4.4%; P=0.008), soluble E-selectin (-5.7%; P=0.02), MMP-9 (-39.6%; P=0.04), soluble phospholipase A2 (-14.8%; P=0.04), and oxidized LDL (-38.4%; P<0.0001). Fenofibrate significantly decreased soluble E-selectin levels only (-6.0,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				P=0.04) and increased soluble phospholipase A2 levels (22.5%; P=0.004). Secondary: Not reported
Hypercholesterolemia Clinical Outcomes Trials (Single Entity Agents)				
Delaying the Progression of Atherosclerosis (Single Entity Agents)				
Nissen et al.[139] (2006) ASTEROID Rosuvastatin 40 mg QD	MC, OL, PRO Patients ≥18 years of age requiring coronary angiography for a stable or unstable ischemic chest pain syndrome or abnormal exercise test, with ≥1 obstruction ≥20% angiographic luminal diameter narrowing in a coronary vessel, not on statin therapy for >3 months within the last 12 months	N=507 24 months	Primary: PAV, absolute change in TAV in the 10 mm subsegment of the coronary artery with the largest plaque volume at baseline Secondary: Change in normalized TAV, lipid parameters	Primary: Rosuvastatin achieved a significant reduction in PAV from baseline (-0.79%; 95% CI, -1.21 to -0.53; P<0.001). Rosuvastatin achieved significant reduction from baseline in atheroma volume in the most diseased 10 mm subsegment (-5.6 mm^3; 95% CI, -6.82 to -3.96; P<0.001). Secondary: Rosuvastatin achieved a significant reduction from baseline in normalized TAV (-12.5 mm^3; 95% CI, -15.08 to -10.48; P<0.001). Rosuvastatin achieved a significant reduction from baseline in the total normalized TAV (-6.8%; 95% CI, -7.82 to -5.60; P<0.001). Rosuvastatin achieved a significant reduction from baseline in TC (33.0%), LDL-C (53.2%), TG (14.5%), LDL-C:HDL-C ratio (58.5%) and non-HDL-C (47.2%; P<0.001). Rosuvastatin achieved a significant increase from baseline in HDL-C (14.7%; P<0.001).
Furberg et al.[140] (1994) ACAPS Lovastatin 20 to 40 mg QD plus warfarin 1 mg QD vs	DB, MC, PC, RCT Asymptomatic patients 40 to 79 years of age, with early carotid atherosclerosis as defined by B-mode ultrasonography and moderately	N=919 3 years	Primary Three year change in the mean maximum IMT in 12 walls of the carotid arteries (near and far walls of the common carotid, the	Primary The progression rate of mean maximum IMT was less with lovastatin plus warfarin than with lovastatin (P=0.04). The overall annualized progression rates of mean maximum IMT with lovastatin and placebo were -0.009 and 0.006 mm/year, respectively (P=0.001). Secondary: The changes in single maximum IMT with lovastatin and placebo were -0.036±0.022 and 0.000±0.011 mm/year, respectively (P=0.12).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
lovastatin 20 to 40 mg QD plus warfarin placebo vs lovastatin placebo plus warfarin 1 mg QD vs lovastatin placebo plus warfarin placebo	elevated LDL-C (between the 60th and 90th percentiles)		bifurcation and the internal carotid arteries on both sides of the neck) Secondary Change in single maximum IMT, incidence of major cardiovascular events and adverse events	Fourteen of the 459 patients receiving lovastatin-placebo had a major cardiovascular event (four CHD deaths, five strokes and five nonfatal MI) compared to five of the 460 patients receiving placebo (P=0.04). There was one death in patients receiving lovastatin and eight in patients receiving lovastatin plus placebo (P=0.02). All six cardiovascular deaths were with lovastatin plus placebo, the remaining three deaths were cancer deaths. Lovastatin and lovastatin-placebo demonstrated no difference in ALT elevations of ≥200% the upper limit of normal.
Byington et al.[141] (1995) PLAC-II Pravastatin 20 mg QD in the evening, titrated up to 40 mg/day vs placebo	DB, PC, RCT Patients with a history of CHD and ≥1 extracranial carotid lesion with the maximum IMT ≥1.3 mm	N=151 3 years	Primary: Change in the mean of maximum IMT measurements in the common, internal and bifurcation carotid artery segments Secondary: Effects on individual carotid artery segments and clinical events	Primary: Pravastatin did not result in a significant reduction in the progression of mean maximum IMT (P=0.44). Pravastatin was associated with a significant 35% reduction in IMT progression in the common carotid artery (P=0.03). There was no significant effect on bifurcation (P=0.49) or on the internal carotid artery (P=0.93) with pravastatin. Secondary: Pravastatin was associated with a 60% reduction in clinical coronary events (P=0.09). When compared to placebo, a significant 61% reduction in the incidence of any coronary events and all-cause mortality was seen with pravastatin (P=0.04).
Yu et al.[142] (2007)	DB, RCT Patients with CHD	N=112 26 weeks	Primary: Improvement in IMT	Primary: Atorvastatin 10 mg was not associated with a significant improvement in either left or right carotid IMT (P value not reported). Atorvastatin 80 mg led

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 80 mg QD vs atorvastatin 10 mg QD	(confirmed by angiographic evidence of coronary stenosis, previous MI, PCI or angina pectoris), hypercholesterolemia and LDL-C >100 mg/dL		Secondary: Reduction in hsCRP level, proinflammatory cytokines at week 26	to a significant improvement in left carotid IMT (P=0.02) as well as the right carotid IMT from baseline (P=0.01). Secondary: Atorvastatin 10 mg was not associated with a significant change in hsCRP (P value not reported). Atorvastatin 80 mg led to a significant reduction in hsCRP level from baseline (P=0.01). Atorvastatin 10 mg was associated with a significant reduction in interleukin-8 (P=0.01), interleukin-18 (P<0.001) and tumor necrosis factor (P<0.001). Atorvastatin 80 mg led to a significant reduction in all the proinflammatory cytokines from baseline (P<0.05).
Schmermund et al.[143] (2006) Atorvastatin 10 mg QD vs atorvastatin 80 mg QD	DB, MC, RCT Patients 32 to 80 years of age without a history of MI, coronary revascularization or hemodynamically relevant stenoses, with moderate calcified coronary atherosclerosis (coronary artery calcification score ≥30), LDL-C 130 to 250 mg/dL in the absence of statin therapy or between 100 to 130 mg/dL under statin therapy, TG <400 mg/dL, ≥2 cardiovascular risk factors	N=471 12 months	Primary: The percent change in total coronary artery calcification volume score Secondary: Change in LDL-C	Primary: There was no significant difference in the primary endpoint between the two treatments (P=0.6477). Secondary: Atorvastatin 80 mg was associated with a 20% reduction in LDL-C compared to atorvastatin 10 mg (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Crouse et al.[144] (2007) METEOR Rosuvastatin 40 mg QD vs placebo	DB, RCT Patients 45 to 70 years of age with LDL-C 120 to 190 mg/dL among patients whose only CHD risk factor was age, and an LDL-C 120 to 160 mg/dL for patients with ≥2 CHD risk factors and a 10 year risk of CHD events of <10%, HDL-C ≤60 mg/dL, TG <500 mg/dL and maximum CIMT 1.2 to 3.5 mm from 2 separate ultrasounds	N=984 2 years	Primary: Annualized rate of change in maximum CIMT of the 12 carotid artery sites (near and far walls of the right and left common carotid artery, carotid bulb and internal carotid artery) Secondary: Annualized rate of change in maximum CIMT of the common carotid artery, carotid bulb and internal carotid artery sites; annualized rate of change in mean CIMT	Primary: Rosuvastatin was associated with a significant reduction in the annualized rate of change in maximum CIMT from baseline compared to placebo (P<0.001). Secondary: Rosuvastatin was associated with a significant 49% reduction in LDL-C from baseline compared to placebo (P<0.001). Rosuvastatin was associated with a significant reduction in the annualized rate of change in the maximum CIMT for the common carotid artery sites (P<0.001), carotid bulb (P<0.001) and internal carotid artery sites (P=0.02) from baseline compared to placebo. Rosuvastatin was associated with a significant reduction in the annualized rate of change in the mean CIMT for the common carotid artery sites (P<0.001) from baseline compared to placebo.
Chan et al.[145] (2010) ASTRONOMER Rosuvastatin 40 mg/day vs	DB, PC, RCT Patients 18 to 82 years of age with asymptomatic mild to moderate aortic stenosis	N=269 3 to 5 years	Primary: Hemodynamic parameters of aortic stenosis severity Secondary: Composite of aortic valve	Primary: Progression of aortic stenosis measured by the peak gradient and aortic valve area did not differ between the two treatments (P values not reported). The mean changes in the peak aortic stenosis gradient, mean gradient and aortic valve area were no significantly different between the two treatments (P=0.32, P=0.49 and P=0.79, respectively). The annual increase in peak aortic stenosis was 6.1±8.2 and 6.3±6.9 mm Hg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo			replacement and cardiac death	with placebo and rosuvastatin (P=0.83). The annual increase in the mean gradient was 3.9±4.9 and 3.8±4.4 mm Hg with placebo and rosuvastatin (P=0.79). The annual decrease in aortic valve area was 0.08±0.21 and 0.07±0.15 cm^2 (P=0.87). The linear mixed models did not show any significant differences in the primary outcomes between the two treatments at any time point during the follow up. Secondary: There were a total of seven cardiac deaths, one of which was associated with aortic valve replacement, and a total of 55 patients with aortic valve replacement. The survival curves of the outcome events (cardiac death or aortic valve replacement) were not significantly different between the two treatments (P=0.45).
Nissen et al.[146] (2004) REVERSAL Atorvastatin 40 mg BID vs pravastatin 40 mg QD	DB, MC, RCT Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long	N=654 18 months	Primary: Percentage change in atheroma volume from baseline Secondary: Nominal change in atheroma volume, nominal change in atheroma volume in the 10 contiguous cross-sections	Primary: Atorvastatin was associated with a significant delay in atheroma volume progression compared to pravastatin (P=0.02). Secondary: Atorvastatin was associated with a significant nominal change in total atheroma volume compared to pravastatin (P=0.02). Atorvastatin was associated with a significant change in the percentage of atheroma volume compared to pravastatin (P<0.001). Atorvastatin was associated with a significant change in atheroma volume in the most severely diseased 10 mm vessel subsegment compared to pravastatin (P=0.01). Progression of coronary atherosclerosis from baseline occurred in 2.7% of pravastatin-treated patients (P=0.001) and none of the atorvastatin-treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			with the greatest and the least atheroma volume	patients (P=0.98). Atorvastatin 80 mg was associated with a significant reduction in TC, LDL-C, TG, apo B and hsCRP (P<0.001) compared to the pravastatin.
Schoenhagen et al.[147] (2006) REVERSAL Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Serial intravascular ultrasound observations from the REVERSAL trial Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long	N=654 18 months	Primary: Percentage change from baseline in external elastic membrane area lesion, lumen area lesion, plaque area lesion and remodeling ratio Secondary: Not reported	Primary: Atorvastatin was associated with a significant 6.6% increase in the external elastic membrane area lesion from baseline (P<0.0001). Atorvastatin was associated with a significant 7.3% increase in the lumen area lesion from baseline (P=0.0002). Atorvastatin was associated with a significant 7.9% increase in the plaque area lesion from baseline (P=0.0002). Atorvastatin was associated with a significant 3.3% reduction in remodeling ratio from baseline (P=0.024). Pravastatin was associated with a significant 9% increase in the external elastic membrane area lesion from baseline (P=0.0002). Pravastatin was associated with a significant 9.5% increase in the lumen area lesion from baseline (P=0.0003). Pravastatin was associated with a significant 9.9% increase in the plaque area lesion from baseline (P=0.0022). Pravastatin was associated with a significant 2.7% reduction in remodeling ratio from baseline (P=0.0013). There was no significant difference between atorvastatin and pravastatin in terms of increase in plaque area from baseline (7.9 vs 9.9%, respectively; P=0.57). There was no significant difference between atorvastatin and pravastatin in terms of reduction in remodeling ratio from baseline (3.3 vs 2.7%, respectively; P=0.68).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported
Nicholls et al.[148] (2006) REVERSAL Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Subanalysis of REVERSAL trial Obese patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI >29.6 kg/m^2 or BMI <29.6 kg/m^2	N=654 18 months	Primary: Percentage change from baseline in lipid parameters, atheroma volume Secondary: Not reported	Primary: Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly lower reduction in TC (40 vs 36%; P=0.007), LDL-C (55 vs 49%; P=0.008) and TG (35 vs 23%; P=0.04). Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly higher reduction in hsCRP (33 vs 40%; P=0.04). There was no significant difference in lipid parameters between the BMI groups among patients randomized to pravastatin (P>0.05). Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly greater benefit on the total atheroma volume (P=0.01) and percent atheroma volume (P=0.0005). In contrast, pravastatin was associated with a significant 6.5% increase in atheroma volume in the obese group (P=0.006). Secondary: Not reported
Nissen et al.[149] (2005) REVERSAL Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Subanalysis of REVERSAL trial evaluating the effect of statin therapy on LDL-C, hsCRP and CAD Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major	N=654 18 months	Primary: Percent change in TC, TG, CRP, non-HDL-C, HDL-C and atheroma volume Secondary: Not reported	Primary: Both treatments achieved a significant reduction from baseline in TC (63%; P<0.001), LDL-C (56%; P<0.001), TG (40%; P=0.002), CRP (22.4%; P<0.001) and non-HDL-C (33%; P<0.001). HDL-C was not significantly increased from baseline with either treatment (4.2%; P=0.11). Atorvastatin exhibited a slower rate of disease progression (atheroma volume) compared to pravastatin (0.2 vs 1.6%; P value not reported). Patients whose LDL-C and hsCRP reductions were greater than the median experienced a significantly slower rate of disease progression compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI >29.6 kg/m^2 or BMI <29.6 kg/m^2			patients with lower LDL-C and hsCRP reductions (P=0.001). Secondary: Not reported
Ikeda et al.[150] (2013) PEACE Moderate (target LDL-C level is 100 mg/dL) vs intensive (target LDL-C level is 80 mg/dL) cholesterol-lowering therapy with pitavastatin	OL, PRO, RCT Patients with CIMT thickening (>1.1 mm) whose LDL-C level was more than 100 mg/dL	N=303 12 months	Primary: Change in mean CIMT Secondary: Change in maximum CIMT	Primary: The intensive pitavastatin therapy resulted in a significant reduction in mean far wall common CIMT (−0.024 mm). In contrast, there was no significant progression or reduction of mean far wall common CIMT in the moderate group (−0.0078 mm). Nevertheless, the difference of mean far wall common CIMT was not statistically significant between the groups (P=0.29). Secondary: Results similar to the primary end point were observed in the secondary end point. The difference of maximum CIMT between the groups did not reach the statistical significance (P=0.07).
Meaney et al.[151] (2009) VYCTOR Pravastatin 40 mg QD (ezetimibe 10 mg/day could be	RCT, OL Patients 40 to 72 years of age with a 10-year absolute risk for coronary death or myocardial	N=90 1 year	Primary: Change in CIMT Secondary: Changes in LDL-C and hsCRP	Primary: After one year, CIMT values were 0.93mm (-30%; P<0.01 vs baseline), 0.90 mm (-30%; P<0.01 vs baseline), and 0.92 mm (-25%; P<0.01 vs baseline) for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively. There was no significant difference among the treatment groups. Secondary: At the end of the study, LDL-C levels were 48, 45, and 48 mg/dL for

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added if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions) vs simvastatin 40 mg QD (dose could be increased to 80 mg/day if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions) vs simvastatin-ezetimibe 20-10 mg QD (dose of simvastatin could be increased to 40 mg/day if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions)	infarction ≥20 according to the ATP III recommendations			pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively (P<0.01 vs baseline for all). There was no significant difference among the treatment groups. The proportion of diabetic patients who attained LDL-C <70 mg/dL at the end of the trial were 62, 80, and 78% for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively (P values not significant). There was no significant difference among the treatment groups. There were no significant differences in hsCRP, HDL-C, TG among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Phan et al.[152] (2014) FATS-OS Combination therapy (lovastatin 40 mg/day, niacin 2 to 3 g/day, and colestipol 20 gm/day for 11 years, then continued with simvastatin 10 to 80 mg/day or lovastatin 40 to 80 mg/day plus niacin 2 to 4 g/day vs conventional therapy (88% single statin therapy)	Case-control study Patients enrolled in the Familial Atherosclerosis Treatment Study (FATS), which randomized 176 men with elevated apo B levels and CAD	N=69 20 years	Primary: Mean common CIMT Secondary: Association between lipids levels and mean common CIMT	Primary: The mean CIMT measured in the combination group was significantly smaller as compared with the usual care group (0.902 ± 0.164 vs 1.056 ± 0.169 mm, P<0.001). Secondary: After 20 years, there were significant changes in lipoprotein levels observed in both groups. The combination therapy group had a greater percent decrease in TC (−42 ± 14 vs −31 ± 17%; P=0.008) and LDL-C (−57 ± 13 vs −38 ± 25%; P<0.001), greater percent increase in HDL-C (38 ± 43 vs 15 ± 23%, P=0.02), and greater decrease in TG (−28 ± 44 vs −1.0 ± 49%, P=0.03) as compared with usual care. CIMT was correlated with combination therapy (−0.154; −0.24 to −0.07; P<0.001), on-therapy LDL-C (0.201; 0.069 to 0.332; P=0.003), and percent change in LDL-C (0.04; 0.005 to 0.091; P=0.03). As compared with the usual care group, the combination treated group had a significantly younger mean vascular age (74.4 ± 16.5 years vs 84.6 ± 13.5 years; P<0.05).
Bays et al.[153,154] (2015) ODYSSEY OPTIONS I Alirocumab 75 mg injected SC every two weeks (dose increased to 150 mg at week 12 if LDL	AC, DB, MC, PG, RCT Patients ≥18 years of age with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥ 100 mg/dL and risk factors for CVE	N=355 24 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: Among atorvastatin 20 and 40 mg regimens respectively, there was a significantly greater decrease in LDL-C with alirocumab add-on from baseline at week 24 compared to add-on ezetimibe, double dose atorvastatin and switching to rosuvastatin (44.1% and 54.0% vs 20.5% and 22.6%, 5.0% and 4.8%, and 21.4%; P<0.001 vs all comparators). Most alirocumab-treated patients (86%) maintained their 75 mg every two weeks regimen. Secondary: Treatment-emergent adverse events occurred in 65.4% of alirocumab patients, compare to 64.4% ezetimibe and 63.8% double atorvastatin/switch to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
≥70 mg/dL) vs ezetimibe 10 mg QD vs atorvastatin (at double baseline dose) vs rosuvastatin 40 mg QD (atorvastatin 40 mg baseline dose cohort only) Prior to randomization, patients were stabilized on atorvastatin 20 mg to 40 mg QD.				rosuvastatin (data pooled).
Farnier et al.[155] (2016) ODYSSEY OPTIONS II Add-on alirocumab 75 mg every 2 weeks (1-mL	DB, DD, MC, RCT Patients with cardiovascular disease and LDL–C ≥70 mg/dL or cardiovascular disease risk factors and LDL–C ≥100	N=305 24 weeks	Primary: Percent change in calculated LDL–C from baseline to 24 weeks Secondary: Percent change	Primary: In the baseline rosuvastatin 10 mg regimen ITT analysis, alirocumab add-on treatment significantly reduced LDL–C levels at Week 24 versus the other comparators (P<0.0001). From baseline, add-on alirocumab reduced LDL–C by 50.6%, add-on ezetimibe reduced LDL–C by 14.4%, and double-dose (20 mg) rosuvastatin reduced LDL–C by 16.3%. In the baseline rosuvastatin 20 mg regimen ITT analysis, mean reductions from baseline in LDL–C at Week 24 were greater in the alirocumab add-on

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
subcutaneous injection via pre-filled pen) vs add-on ezetimibe 10 mg/day vs double-dose rosuvastatin All patients received baseline rosuvastatin regimens (10 or 20 mg)	mg/dL		from baseline in calculated LDL–C on-treatment at Week 24 in the modified ITT (mITT) population (on-treatment analysis), percent change in LDL–C from baseline to Week 12 (ITT and on-treatment), the percent change in other lipid parameters, and the proportion of very-high and high CV risk patients reaching LDL–C <70 mg/ or <100 mg/ at Week 24, respectively, in both ITT and on-treatment analyses; Safety	group versus the other comparators. LDL–C reductions were 36.3% in the add-on alirocumab group, compared with 11.0% in the add-on ezetimibe group (P=0.0136) and with 15.9% in the double-dose (40 mg) rosuvastatin group (P=0.0453). However, the pre-specified threshold P-value for these 4-way comparisons was 0.0125; therefore, both primary comparisons failed to reach statistical significance in the baseline rosuvastatin 20 mg regimen. Secondary: As a result of both primary comparisons failing to reach statistical significance, all key secondary efficacy endpoints were not tested for statistical significance with respect to the two comparisons in the baseline rosuvastatin 20 mg regimen. In the baseline rosuvastatin 10 mg regimen groups, the proportion of patients at very-high and high CV risk who reached a LDL–C level of <70 mg/dL or <100 mg/dL at Week 24, depending on risk status, was significantly greater in the alirocumab add-on group (84.9%) compared with the ezetimibe add-on group (57.2%; P=0.0007) and the rosuvastatin 20 mg group (45.0%; P<0.0001). The proportion of patients who reached the more stringent LDL–C level of <70 mg/dL at Week 24 was also significantly greater in the alirocumab add-on group (77.8%) compared with the ezetimibe add-on and rosuvastatin 20 mg groups (43.1%; P<0.0001 and 31.3%; P<0.0001), respectively. Treatment-emergent adverse events occurred in 56.3% of alirocumab patients versus 53.5% ezetimibe and 67.3% double-dose rosuvastatin (pooled data).
Moriarty et al.[156] (2015) ODYSSEY ALTERNATIVE Alirocumab 75	AC, DB, MC, PG, RCT Patients with primary hypercholesterole	N=314 24 weeks	Primary: Percent change in calculated LDL–C from baseline to 24 weeks	Primary: For the primary ITT efficacy analysis, LS mean change in LDL-C concentrations from baseline to week 24 were −45.0% for alirocumab and −14.6% for ezetimibe, with a difference between groups of −30.4% (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg SC every 2 weeks vs ezetimibe 10 mg/ day vs atorvastatin 20 mg/ day	mia at moderate to high cardiovascular risk with statin intolerance (unable to tolerate ≥2 statins, including one at the lowest approved starting dose) due to muscle symptoms		Secondary: Change from baseline to 24 weeks using on-treatment (modified ITT) LDL-C values, and percent change from baseline to 12 and 24 weeks in LDL-C, apolipoprotein B, non–HDL-C, total cholesterol, lipoprotein(a), HDL-C, apolipoprotein A1, and fasting triglyceride concentrations; adverse events	Secondary: For the on-treatment analysis, the change from baseline was −52.2% for alirocumab and −17.1% for ezetimibe (LS mean difference of −35.1%; P<0.0001). A substantial reduction in LDL-C concentration occurred over the first four weeks, which was greater in the alirocumab arm and persisted throughout the 24-week treatment period. At week 24, 52 (41.9%) patients on alirocumab and 5 (4.4%) of those on ezetimibe (P<0.0001; ITT analysis) reached an LDL-C goal of <70 mg/dL in very high cardiovascular risk patients or <100 mg/dL in moderate-to-high-risk patients. Corresponding results in the on-treatment population were 51.2% and 5.6% (P<0.0001). The greater effect of alirocumab relative to ezetimibe on LDL-C-lowering from baseline to week 24 was consistent across most of the prespecified subgroups in the ITT population. In addition, reductions in apolipoprotein B, non–HDL-C, total cholesterol and lipoprotein(a) concentrations were greater for alirocumab vs ezetimibe (all P<0.0001). There were no statistically significant differences between the two groups in changes in triglyceride, HDL-C, and apolipoprotein A1 concentrations. Overall rates of treatment-emergent and serious AEs were generally similar between treatment arms, and there were no deaths in the study.
Primary Prevention of Coronary Heart Disease (Single Entity Agents)				
Knopp et al.[157] (2006) ASPEN Atorvastatin 10 mg QD vs placebo	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes for ≥3 years prior to screening, LDL-C ≤140 (if they had a history of an MI or an interventional procedure >3 months before	N=2,410 4 years	Primary: Time to occurrence of the composite clinical endpoint including cardiovascular death, nonfatal MI, nonfatal stroke, recanalization,	Primary: There was no significant difference between the two treatments in the time to first primary event (HR, 90; 95% CI, 0.73 to 1.12; P=0.034). Less patients receiving atorvastatin experienced the primary endpoints compared to patients receiving placebo (13.7 vs 15.0%; P=0.034). Secondary: Atorvastatin was associated with a significant decrease in LDL-C compared to placebo (29.0 vs 1.6%; P<0.0001). Among patients without a prior history of an MI or interventional procedure,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	screening) or ≤160 mg/dL, TG ≤600 mg/dL		CABG surgery, resuscitated cardiac arrest or worsening or unstable angina requiring hospitalization Secondary: Time to occurrence of cardiovascular death, noncardiovascular death, TIA, worsening or unstable angina not requiring hospitalization, worsening or unstable angina requiring hospitalization, surgery for newly diagnosed PAD and acute ischemic heart failure requiring hospitalization; cholesterol level reduction; safety	10.4 and 10.8% of atorvastatin- and placebo-treated patients experienced a primary endpoint (HR, 97; 95% CI, 0.74 to 1.18). Among patients with a prior history of an MI or interventional procedure, 26.2 and 30.8% of atorvastatin- and placebo-treated patients experienced a primary endpoint (HR, 82; 95% CI, 0.59 to 1.15). RR reductions in fatal and nonfatal MI were 27% overall (P=0.10), 19% for patients treated for primary protection (P=0.41) and 36% for patients treated for secondary protection (P=0.11). Adverse events were similar in both treatments for the total, primary and secondary prevention groups (P value not reported). Serious adverse events occurred in 37.7 and 35.4% of atorvastatin- and placebo-treated patients (P value not reported).
Colhoun et al.[158] (2004) CARDS	DB, MC, RCT Patients 40 to 75	N=2,838 3.9 years	Primary: Incidence of major	Primary: Atorvastatin led to a significant 37% reduction in the RR of the primary endpoint compared to placebo (95% CI, 17 to 52; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 10 mg/day vs placebo All patients were randomized after a 6 week placebo lead in period.	years of age with type 2 diabetes without a history of CHD, LDL-C ≤160 mg/dL, TG ≤600 mg/dL and ≥1 other CHD risk factor		cardiovascular events (CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) Secondary: All-cause mortality, acute hospital-verified cardiovascular endpoint (major cardiovascular disease events, angina, TIA, peripheral vascular disease requiring hospitalization or surgery), reduction in coronary revascular-ization, lipid reduction	Secondary: Atorvastatin led to a significant 27% reduction in the RR of all-cause mortality compared to placebo (95% CI, 1 to 48; P=0.059). Atorvastatin led to a significant 32% reduction in the RR of any cardiovascular endpoint compared to placebo (95% CI, 15 to 45; P=0.001). Atorvastatin was associated with a significant reduction in stroke compared to placebo (1.5 vs 2.8%; HR, 0.52; 95% CI, 0.31 to 0.89). Atorvastatin was not associated with a significant reduction in coronary revascularization compared to placebo (HR, 0.69; 95% CI, 0.41 to 1.16). Atorvastatin was associated with a significant 40% reduction in baseline LDL-C compared to placebo (P<0.0001). Atorvastatin was associated with a significant 26% reduction in baseline TC levels compared to placebo (P<0.0001). Atorvastatin was associated with a significant one percent increase in baseline HDL-C compared to placebo (P=0.0002). Atorvastatin was associated with a significant 36% reduction in baseline non-HDL-C compared to placebo (P<0.0001). Atorvastatin was associated with a significant 19% reduction in baseline TG compared to placebo (P<0.0001). Atorvastatin was associated with a significant 23% reduction in baseline apo B compared to placebo (P<0.0001). The frequency of adverse events was similar between the two treatments (P value not reported).
Neil et al.[159] (2006) CARDS	Post hoc analysis of CARDS	N=2,838 3.9 years	Primary: Major cardiovascular	Primary: Atorvastatin led to a significant 38% reduction in the RR of the primary endpoint in patients ≥65 years of age (95% CI, 8 to 58; ARR, 3.9%, P=0.017).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 10 mg/day vs placebo All patients were randomized after a 6 week placebo lead in period.	Adult patients with type 2 diabetes without a history of CHD, LDL-C ≤160 mg/dL, TG ≤600 mg/dL and ≥1 other CHD risk factor; stratified by age (≥65 years of age)		events (acute CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) among patients ≥65 and <65 years of age Secondary: All-cause mortality, acute hospital-verified cardiovascular endpoint (major cardiovascular disease events, angina, TIA, peripheral vascular disease requiring hospitalization or surgery) among patients ≥65 and <65 years of age	Consequently, 21 patients would need to be treated for four years to prevent one major cardiovascular event. Atorvastatin led to a significant 37% reduction in the RR of the primary endpoint in patients <65 years of age (95% CI, 7 to 57; ARR, 2.7%; P=0.019). Consequently, 33 patients would need to be treated for four years to prevent one major cardiovascular event. Secondary: There was no significant effect on all-cause mortality in either the <65 (P=0.98) or the ≥65 year old population (P=0.245). Atorvastatin led to a significant reduction in LDL-C among both the younger and the older patients compared to placebo (38 and 41%, respectively; P<0.001). Atorvastatin led to a significant reduction in TC among both the younger and the older patients compared to placebo (26 and 27%, respectively; P<0.001). Atorvastatin led to a significant reduction in TG among both the younger and the older patients compared to placebo (P<0.001). The frequency of adverse events was similar between the two treatments (P value not reported).
Hitman et al.[160] (2007) CARDS	Subanalysis of CARDS	N=2,838 3.9 years	Primary: Fatal or nonfatal stroke,	Primary: Atorvastatin was associated with a significant 48% reduction in stroke compared to placebo (1.5 vs 2.5%; HR, 0.52; 95% CI, 0.31 to 0.89; P=0.016).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 10 mg/day vs placebo All patients were randomized after a 6 week placebo lead in period.	Patients 40 to 75 years of age with type 2 diabetes without a history of CHD, LDL-C ≤160 mg/dL, TG ≤600 mg/dL and ≥1 other CHD risk factor		type of stroke, risk factors for stroke Secondary: Not reported	Atorvastatin was associated with a significant 50% reduction in non-hemorrhagic stroke compared to placebo (1.1 vs 2.2%; HR, 0.50; 95% CI, 0.27 to 0.91; P=0.024). Atorvastatin was associated with a significant 42% reduction in stroke or TIAs compared to placebo (2.1 vs 3.6%; HR, 0.58; 95% CI, 0.37 to 0.92; P=0.019). Independent risk factors predicting stroke were age (HR, 2.3; P<0.001), microalbuminuria (HR, 2.0; P=0.007) and glycemic control (HR, 2.7; P=0.007). Women were at a lower risk for stroke than men (HR, 0.3; P=0.004). Secondary: Not reported
Sever et al.[161] (2003) ASCOT-LLA Atorvastatin 10 mg/day vs placebo All patients received antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach SBP and DBP goals of <140	DB, MC, RCT Patients 40 to 79 years of age with either untreated or treated HTN, TC ≤6.5 mmol/L and not currently taking a statin or a fibrate; patients were also required to have >3 of the following cardiovascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes type 2, PAD, previous stroke or TIA, age	N=10,305 3.3 years	Primary: Combined endpoint of nonfatal MI and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal heart failure, fatal and nonfatal stroke, total coronary endpoints, total cardiovascular	Primary: Atorvastatin was associated with a significant 36% reduction in the primary endpoint compared to placebo (HR, 0.64; 95% CI, 0.50 to 0.83; P=0.0005). Secondary: Atorvastatin was associated with a significant 38% reduction in the primary endpoint, excluding silent MIs, compared to placebo (HR, 0.62; 95% CI, 0.47 to 0.81; P=0.0005). Atorvastatin was not associated with a significant reduction in all-cause mortality (P=0.1649), cardiovascular mortality (P=0.5066) or fatal and nonfatal heart failure (P=0.5794) compared to placebo. Atorvastatin was associated with a significant 27% reduction in the risk for fatal and nonfatal strokes compared to placebo (HR, 0.73; 95% CI, 0.56 to 0.96; P=0.0236). Atorvastatin was associated with a significant 29% reduction in the risk for total coronary events compared to placebo (HR, 0.71; 95% CI, 0.59 to 0.86; P=0.005). Atorvastatin was associated with a significant 21% reduction in the risk for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
and 90 mm Hg, respectively).	>55 years, microalbuminuria or proteinuria, male sex, smoking, TC:HDL-C >6 or family history of CHD		events and procedures	total cardiovascular events and procedures compared to placebo (HR, 0.79; 95% CI, 0.69 to 0.90; P=0.0005).
Sever et al.[162] (2005) ASCOT-LLA Atorvastatin 10 mg/day vs placebo All patients received antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach SBP and DBP goals of <140 and 90 mm Hg, respectively).	2 year extension of ASCOT-LLA Patients 40 to 79 years of age with either untreated or treated HTN, TC ≤6.5 mmol/L and not currently taking a statin or a fibrate; patients were also required to have >3 of the following cardio-vascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes type 2, PAD, previous stroke or TIA, age >55 years, microalbuminuria or proteinuria, male sex, smoking, TC:HDL-C >6 or family history of CHD	N=10,305 5.5 years	Primary: Combined endpoint of nonfatal MI and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, total coronary endpoints, total cardiovascular events	Primary: Atorvastatin was associated with a significant 36% reduction in the primary endpoint compared to placebo (HR, 0.64; 95% CI, 0.53 to 0.78; P≤0.0001). Secondary: Atorvastatin was associated with a significant 37% reduction in the primary endpoint, excluding silent MIs, compared to placebo (HR, 0.63; 95% CI, 0.51 to 0.77; P≤0.0001). Atorvastatin was associated with a significant 15% reduction in the risk for all-cause mortality compared to placebo (HR, 0.85; 95% CI, 0.74 to 0.98; P=0.0219). Atorvastatin was not associated with a significant reduction in cardiovascular mortality (P=0.1281), or fatal and nonfatal heart failure (P=0.9809) compared to placebo. Atorvastatin was associated with a significant 23% reduction in the risk for fatal and nonfatal strokes compared to placebo (HR, 0.77; 95% CI, 0.63 to 0.95; P=0.0127). Atorvastatin was associated with a significant 27% reduction in the risk for total coronary events compared to placebo (HR, 0.73; 95% CI, 0.63 to 0.85; P≤0.0001). Atorvastatin was associated with a significant 19% reduction in the risk for total cardiovascular events and procedures compared to placebo (HR, 0.81; 95% CI, 0.73 to 0.89; P≤0.0001).
Downs et al.[163]	DB, MC, PC, RCT	N=6,605	Primary	Primary

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(1998) AFCAPS/TexCAPS Lovastatin 20 to 40 mg QD vs placebo	Men 45 to 73 years of age and postmenopausal women 55 to 73 years of age on a low-saturated fat, low-cholesterol diet with TC 180 to 264 mg/dL, LDL-C 130 to 190 mg/dL, HDL ≤45 mg/dL for men or ≤47 mg/dL for women and TG ≤400 mg/dL, without a prior history of MI, angina, claudication, cerebrovascular accident or TIA; patients with LDL-C 125 to 129 mg/dL were included when TC:HDL-C >6	5.2 years	First acute major coronary event (fatal or nonfatal MI, unstable angina or sudden cardiac death) Secondary Fatal or nonfatal coronary revascularization procedure, unstable angina, fatal or nonfatal MI, fatal or nonfatal cardiovascular events, fatal or nonfatal coronary events, cardiovascular mortality and CHD mortality, total mortality, fatal and nonfatal cancer, safety, discontinuation rates	After an average follow up of 5.2 years, lovastatin was associated with a significant 37% lower incidence of the first acute major coronary event compared to placebo (95% CI, 0.50 to 0.79; P<0.001). Secondary Lovastatin was associated with a significant 33% reduction in revascularization (95% CI, 0.52 to 0.85; P=0.001), 32% reduction in unstable angina (95% CI, 0.49 to 0.95; P=0.02), 40% reduction in the incidence of fatal or nonfatal MI (95% CI, 0.43 to 0.83; P=0.002), 25% reduction in fatal or nonfatal cardiovascular events (95% CI, 0.62 to 0.91; P=0.003) and 25% reduction in fatal or nonfatal coronary events (95% CI, 0.61 to 0.92; P=0.006) compared to placebo. There were too few events to perform survival analysis on cardiovascular (1.0 vs 1.4%) and CHD mortality (0.6 vs 0.8%) events based on prespecified criteria. The overall mortality rate and fatal and nonfatal cancer rates were similar between the two treatments (P value not reported). Discontinuation rates due to adverse events were 13.6 and 13.8% with lovastatin and placebo (P value not reported). Both treatments had similar rates of serious adverse events (34.2 vs 34.1%; P value not reported).
Schouten et al.[164] (2009) DECREASE III Fluvastatin XL	RCT, DB, PC Patients ≥40 years of age who were scheduled for	N=497 ≥30 days post-surgery	Primary: Occurrence of myocardial ischemia	Primary: Myocardial ischemia occurred in 10.8% of patients in the fluvastatin XL group within 30 days after surgery compared to 19.0% of patients in the placebo group (HR, 0.55; 95% CI, 0.34 to 0.88; P=0.01). The number of patients who would need to be treated to prevent 1 patient from having myocardial ischemia

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
80 mg QD prior to surgery vs placebo Patients in both groups also received beta-blocker therapy prior to surgery	noncardiac vascular surgery (abdominal aortic aneurysm repair, distal aortoiliac reconstruction, lower-limb arterial reconstruction, or carotid-artery endarterectomy) who were statin naïve		Secondary: Composite of death from cardiovascular causes and nonfatal MI	was 12. Secondary: The composite of death from cardiovascular causes or nonfatal myocardial infarction occurred in 4.8% of patients receiving fluvastatin XL compared to 10.1% of patients receiving placebo (HR, 0.47; 95% CI, 0.24 to 0.94; P=0.03). The number of patients who would need to be treated to prevent the composite end point of death from cardiovascular causes or nonfatal MI in one patient was 19.
No authors listed.[165] (2002) ALLHAT-LLT Pravastatin 40 mg/day vs usual care Vigorous cholesterol-lowering therapy in the usual care group was discouraged.	MC, OL, RCT Patients ≥55 years of age, with Stage 1 or 2 HTN, ≥1 additional CHD risk factor, fasting LDL-C 120 to 189 mg/dL for patients with no known CHD or 100 to 129 mg/dL for patients with known CHD and fasting TG <350 mg/dL	N=10,355 Mean, 4.8 years (maximum 7.8 years)	Primary: All-cause mortality Secondary: Composite of fatal CHD or nonfatal MI, cause-specific mortality, total and site-specific cancers	Primary: All-cause mortality did not differ significantly between the two treatments (RR, 0.99; 95% CI, 0.89 to 1.11; P=0.88). Secondary: Rates of CHD (fatal CHD plus nonfatal MI) and stroke were slightly lower with pravastatin compared to usual care (RR, 0.91; 95% CI, 0.79 to 1.04; P=0.16). There were 209 total strokes with pravastatin and 231 total strokes with usual care (RR, 0.91; 95% CI, 0.75 to 1.09; P=0.31). Heart failure rates were similar between the two treatments (RR, 0.99; 95% CI, 0.83 to 1.18; P=0.89). The six year cancer rates were similar between the two treatments (RR, 1.03; 95% CI, 0.89 to 1.19; P=0.66).
Nakamura et al.[166] (2006) MEGA Pravastatin 10 to	OL, PRO, RCT Patients 40 to 70 years of age weighing ≥40 kg, with	N=8,214 Mean 5.2 years	Primary: CHD incidence, sudden cardiac deaths, MIs, coronary re-vascularization	Primary: Pravastatin plus diet was associated with a significant reduction in the incidence of CHD compared to diet (3.3 vs 5.0%; HR, 0.67; 95% CI, 0.49 to 0.91; P=0.01). There was no significant difference between the two treatments in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
20 mg/day plus NCEP step I diet vs NCEP step I diet	hypercholesterolemia, without a history of CHD or FH		Secondary: CHD and cerebral infarction, all cardiovascular events, strokes, all-cause mortality	incidence of sudden cardiac deaths or anginal episodes (P>0.05 for both). Secondary: Pravastatin plus diet was associated with a significant reduction in the incidence of MIs compared to diet (0.9 vs 1.6%; HR, 0.52; 95% CI, 0.29 to 0.94; P=0.03). Pravastatin plus diet was associated with a significant reduction in the incidence of coronary revascularizations compared to diet (2.0 vs 3.2%; HR, 0.60; 95% CI, 0.41 to 0.89; P=0.01). Secondary: Pravastatin plus diet was associated with a significant reduction in the incidence of CHD and cerebral infarctions compared to diet (5.0 vs 7.1%; HR, 0.70; 95% CI, 0.54 to 0.90; P=0.005). Pravastatin plus diet was associated with a significant reduction in the incidence of all cardiovascular events compared to diet (6.4 vs 8.5%; HR, 0.74; 95% CI, 0.59 to 0.94; P=0.01). There was no significant difference between the two treatments in all-cause mortality or the incidence of strokes (P>0.05 for both).
No authors listed.[167] (1993) PMS-CRP Pravastatin 20 to 40 mg/day vs placebo	DB, MC, PC, RCT Adult patients with hypercholesterolemia	N=1,062 26 weeks	Primary: Lipid levels at 13 and 26 weeks, occurrence of cardiovascular events Secondary: Not reported	Primary: After 13 weeks, pravastatin was associated with significant reductions in LDL-C (26%), TC (19%) and TG (12%) and significant elevations in HDL-C (7%) compared to placebo (P<0.001 for all). Throughout the 26 weeks, there were no differences in the total incidence of clinical adverse events between the two treatments. No MIs or cerebral infarctions occurred with pravastatin, and a total of six MIs and three cerebral infarctions occurred with placebo (P value not reported). Secondary: Not reported
Shepherd et al.[168] (1995) WOSCOPS	DB, PC Men 45 to 64 years	N=6,595 4.9 years	Primary: Incidence of nonfatal MI or	Primary: Pravastatin was associated with a significant 31% reduction in the risk of the combined primary endpoint of definite nonfatal MI and death from CHD (95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Pravastatin 40 mg/day vs placebo	of age with hypercholesterolemia and no history of MI		death from CHD as a first event Secondary: Incidence of death from CHD and nonfatal MI	CI, 17 to 43; P<0.001) compared to placebo. The absolute difference in the risk at five-years was 2.4%. Secondary: The reduction in the risk of nonfatal MI with pravastatin was significant whether the definite cases of MI were considered alone or in combination with suspected cases (P≤0.001). In the analysis of both definite and suspected cases of death from CHD, there was a significant risk reduction of 33% with pravastatin (95% CI, 1 to 55; P=0.042), but not in the analysis of definite cases alone (P value not reported). When the effect of pravastatin on death from all cardiovascular causes was analyzed, a 32% risk reduction was observed (95% CI, 3 to 53; P=0.033). Additionally, pravastatin was associated with a significant 31% reduction in the frequency of coronary angiography (95% CI, 10 to 47; P=0.007) and a 37% reduction in the frequency of revascularization procedures (95% CI, 11 to 56; P=0.009) compared to placebo.
Ford et al.[169] (2007) WOSCOPS Pravastatin 40 mg/day vs placebo	ES of WOSCOPS Men 45 to 64 years of age with hypercholesterolemia and no history of MI	N=6,595 15 years of total follow-up	Primary: Mortality from CHD or nonfatal MI, CHD, cardiovascular causes, all-cause mortality Secondary: Not reported	Primary: Pravastatin was associated with a significant reduction in the risk of death from CHD or nonfatal MI compared to placebo over a 15 year period (11.8 vs 15.5%; HR, 0.73; 95% CI, 0.63 to 0.83; P<0.001). Pravastatin was associated with a significant reduction in the risk of death from all causes compared to placebo over a 15 year period (18.7 vs 20.5%; HR, 0.88; 95% CI, 0.79 to 0.99; P=0.03). Pravastatin was associated with a significant reduction in the risk of death from cardiovascular causes compared to placebo over a 15 year period (7.6 vs 9.0%; HR, 0.81; 95% CI, 0.68 to 0.96; P=0.01). Pravastatin was associated with a significant reduction in the risk of death from CHD compared to placebo over a 15 year period (5.1 vs 6.3%; HR, 0.78; 95% CI, 0.64 to 0.96; P=0.02). Pravastatin was associated with a small increase in the risk of death from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				stroke compared to placebo over a 15 year period (1.6 vs 1.1%; HR, 1.37; 95% CI, 0.90 to 2.09; P=0.14). Secondary: Not reported
Vallejo-Vaz et al.[170] (2017) WOSCOPS Pravastatin 40 mg/day vs placebo	Post-hoc analysis Men 45 to 64 years of age with LDL-C ≥190 mg/dL without pre-existing vascular disease at baseline	N=5,529 20 years	Primary: Coronary heart disease (definite or suspected nonfatal MI plus definite or suspected coronary heart disease death) and major adverse cardiovascular events (composite of cardiovascular death, nonfatal MI, and nonfatal stroke) were assessed over the 4.9-year RCT phase Secondary: Mortality outcomes over a total of 20 years of observational follow-up	Primary: Among individuals with LDL-C ≥190 mg/dL, pravastatin reduced the risk of coronary heart disease by 27% (P=0.033) with a 25% risk reduction in major adverse cardiovascular events (P=0.037) compared to placebo. Secondary: In the 20-year follow-up, all-cause mortality occurred in 36.11% of placebo patients and 30.72% of pravastatin patients (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.004).
Han et al.[171] (2017)	Post-hoc analysis	N=2,867	Primary: All-cause	Primary: The hazard ratios for all-cause mortality in the pravastatin group vs the usual

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ALLHAT-LLT Pravastatin 40 mg/day vs usual care	Ambulatory adults ≥65 years of age with hypertension and without baseline atherosclerotic cardiovascular disease	6 years	mortality Secondary: Cause-specific mortality and nonfatal MI or fatal coronary heart disease combined (coronary heart disease events)	care group were 1.18 (95% CI, 0.97 to 1.42; P=0.09) for all adults 65 years and older, 1.08 (95% CI, 0.85 to 1.37; P=0.55) for adults aged 65 to 74 years, and 1.34 (95% CI, 0.98 to 1.84; P =0.07) for adults 75 years and older. Secondary: There was no significant difference between groups for any of the secondary outcomes.
Ridker et al.[172] (2008) JUPITER Rosuvastatin 20 mg/day vs placebo	DB, MC, PC, RCT Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL	N=17,802 1.9 years	Primary: Incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial re-vascularization procedure or confirmed death from cardiovascular causes) Secondary: Individual components of the primary endpoint, all-cause mortality	Primary: At the time of trial termination (median follow up, 1.9 years; maximal follow up, 5.0 years), 142 first major cardiovascular events had occurred with rosuvastatin compared to 251 first major cardiovascular events with placebo. The rates of the primary endpoint were 0.77 and 1.36 per 100 persons-years of follow up with rosuvastatin and placebo, respectively (HR for rosuvastatin, 0.56; 95% CI, 0.46 to 0.69; P<0.00001). The number of patients who would need to be treated with rosuvastatin for two years to prevent the incidence of one primary endpoint is 95, and the NNT for four years is 31. Secondary: Rosuvastatin was associated with significant reductions in rates of the individual components of the primary endpoint. The corresponding rates per 100 persons-years of follow up for the individual endpoints with rosuvastatin and placebo were: 0.17 and 0.37 for fatal or nonfatal MI (HR, 0.46; 95% CI, 0.30 to 0.70; P=0.0002); 0.18 and 0.34 for fatal or nonfatal stroke (HR, 0.52; 95% CI, 0.34 to 0.79; P=0.002); 0.41 and 0.77 for revascularization or unstable angina (HR, 0.53; 95% CI, 0.40 to 0.70; P<0.00001) 0.45 and 0.85 for the combined endpoint of MI, stroke or death from cardiovascular causes (HR, 0.53; 95% CI, 0.40 to 0.69; P<0.00001) and 1.00 and 1.25 for death from any cause (HR, 0.80; 95% CI, 0.67 to 0.97; P=0.02). In analyses limited to deaths for which the date of death was known with certainty, there was a similar reduction in the HR associated with rosuvastatin (0.81; 95% CI, 0.67 to 0.98; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				For patients with elevated hsCRP levels but no other major risk factor other than increased age, the benefit of rosuvastatin was similar to that for higher risk patients (HR, 0.63; 95% CI, 0.44 to 0.92; P=0.01).
Everett et al.[173] (2001) JUPITER Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL	N=17,802 1.9 years (maximum, 5.0 years)	Primary: Incidence of stroke Secondary: Not reported	Primary: At the time of trial termination, 33 and 64 strokes occurred in patients receiving rosuvastatin and placebo. Rosuvastatin resulted in a 48% reduction in the HR of fatal and nonfatal stroke compared to placebo (incidence rate, 0.18 vs 0.34 per 100 person-years; HR, 0.52; 95% CI, 0.34 to 0.79; P=0.002), a finding that was consistent across all examined subgroups. This finding was due to a 51% reduction in the rate of ischemic stroke (HR, 0.49; 95% CI, 0.30 to 0.81; P=0.004), with no difference in the rates of hemorrhagic stroke (HR, 0.67; 95% CI, 0.24 to 1.88; P=0.44). TIAs were observed with similar frequency in the two treatments (HR, 0.93; 95% CI, 0.56 to 1.56; P=0.79). The projected NNT for five-years to prevent one stroke was 123. Secondary: Not reported
Koenig et al.[174] (2001) JUPITER Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL; patients with high global cardiovascular risk (10 year Framingham risk	N=17,802 (9 and 52% were considered to be high risk based on 10 year Framingham risk score and 10 year European systematic coronary risk evaluation) 1.9 years (maximum, 5.0 years)	Primary: Incidence of first MI, stroke or cardiovascular death; first incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularizatio n procedure or confirmed	Primary: Patients with a 10 year Framingham risk score >20% the rate of the combined endpoint of MI, stroke or cardiovascular death was 9.4 and 18.2 per 1,000 person-years with rosuvastatin and placebo (HR, 0.50; 95% CI, 0.27 to 0.93; P=0.028). Rosuvastatin had no significant effect on the incidence of major cardiovascular events (P=0.155) and all-cause mortality (P=0.193). Among patients with a 10 year European systematic coronary risk evaluation ≥5%, the corresponding rates were 6.9 vs 12.0 using a model extrapolating risk for age ≥65 years (HR, 0.57; 95% CI, 0.43 to 0.78; P=0.0003) and rates were 5.9 vs 12.7 when risk for age was capped at 65 years of age (HR, 0.47; 95% CI, 0.32 to 0.68; P<0.0001). Rosuvastatin significantly reduced the incidence of major coronary events (P=0.0003) but not all-cause mortality (P=0.076) in patients with a 10 year European systematic coronary risk evaluation ≥5% extrapolating risk for age ≥65 years. When the risk for age was capped at 65 years of age, rosuvastatin had significant effect on the incidence of major cardiovascular events (P<0.0001) and all-cause mortality (P=0.022).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	score >20% and 10 year European systematic coronary risk evaluation ≥5%)		death from cardiovascular causes); all-cause mortality Secondary: Not reported	Secondary: Not reported
Ridker et al.[175] (2010) JUPITER Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL; stratified by kidney function (eGFR <60 mL/min and eGFR ≥60 mL/min)	N=17,802 (n=3,267 with moderate CKD) 1.9 years (maximum, 5.0 years)	Primary: Incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure or confirmed death from cardiovascular causes), all-cause mortality Secondary: Individual components of the primary endpoint, all-cause mortality	Primary: Among patients with eGFR <60 mL/min, the incidence rate of the primary endpoint was significantly lower with rosuvastatin compared to placebo (incidence rate, 1.08 vs 1.95 per 100 person-years; HR, 0.55; 95% CI, 0.38 to 0.82; P=0.002). Irrespective of treatment, at trial end 111 and 282 patients with eGFR <60 and ≥60 mL/min suffered a primary endpoint (incidence rate, 1.51 vs 0.95 per 100 person-years; HR, 1.54; 95% CI, 1.23 to 1.92; P=0.0002). Secondary: Among patients with eGFR <60 mL/min, rosuvastatin significantly reduced the rate of MI (incidence rate, 0.21 vs 0.54 per 100 person-years; HR, 0.40; 95% CI, 0.17 to 0.90; P=0.02), arterial revascularization (0.51 vs 1.07; HR, 0.48; 95% CI, 0.28 to 0.83; P=0.006), the combined MI, stoke or confirmed cardiovascular death (0.64 vs 1.09; HR, 0.59; 95% CI, 0.36 to 0.99; P=0.04), venous thromboembolism (0.16 vs 0.46; HR, 0.14 to 0.88; P=0.02), all-cause mortality (0.85 vs 1.53; HR, 0.56; 95% CI, 0.37 to 0.85; P=0.005), combined primary endpoint plus any death (1.72 vs 3.13; HR, 0.55; 95% CI, 0.41 to 0.75; P=0.0001) and the primary endpoint plus VTE plus any death (1.86 vs 3.51; HR, 0.53; 95% CI, 0.40 to 0.71; P<0.0001) compared to placebo. Among patients with eGFR <60 mL/min, rosuvastatin demonstrated no benefit compared to placebo in reducing the risk of stroke (incidence rate, 0.27 vs 0.38 per 100 person-years; HR, 0.71; 95% CI, 0.31 to 1.59; P=0.40).
Ridker et al.[176] (2009) JUPITER Rosuvastatin 20	Post hoc analysis of JUPITER Men ≥50 years of age and women	N=17,802 1.9 years (maximum, 5 years)	Primary: Incidence of a first major cardiovascular event	Primary: For the endpoint of MI, stroke, revascularization or death, the five-year NNT was 20 (95% CI, 14 to 34). All subgroups had five-year NNTs for this combined endpoint below 50 (men, 17; women, 31; whites, 21; nonwhites, 19; BMI ≤25 kg/m^2, 18; BMI >25 kg/m^2, 21; with or without a family history of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day vs placebo	≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL		Secondary: Not reported	coronary disease, 9 and 6; with or without metabolic syndrome, 19 and 22; estimated 10 years Framingham risk >10% and <10%, 14 and 37). For the combined primary endpoint plus VTE, the five-year NNT was 18 (95%; 13 to 29). For the endpoint of MI, stroke or death, the five-year NNT was 29 (95% CI, 19 to 56). In sensitivity analyses addressing the theoretical utility of alternative agents, five-year NNT values of 38 and 57 were estimated for statin regimens that deliver 75 and 50% of the relative benefit observed in JUPITER, respectively. Secondary: Not reported
Yusuf et al.[177] (2016) HOPE-3 Rosuvastatin 10 mg/day vs placebo	DB, MC, RCT Men ≥55 years of age and women ≥65 years of age who did not have cardiovascular disease and were at intermediate risk (defined as an annual risk of major cardiovascular events of approximately 1%)	N=12,705 Median 5.6 years	Primary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and second coprimary outcome of composite of revascularization, heart failure, and resuscitated cardiac arrest Secondary: Death from any cause, the components of the coprimary	Primary: The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (haHR, 0.76; 95% CI, 0.64 to 0.91; P=0.002; NNT with rosuvastatin to prevent one coprimary outcome event, 91). The second coprimary outcome occurred in 277 participants (4.4%) in the rosuvastatin group and in 363 participants (5.7%) in the placebo group (HR, 0.75; 95% CI, 0.64 to 0.88; P<0.001; NNT, 73). Secondary: Significantly fewer participants in the rosuvastatin group than in the placebo group had strokes. Fewer ischemic strokes occurred in the rosuvastatin group than in the placebo group (41 vs 77), but slightly more hemorrhagic strokes occurred (11 vs 8), and the same number of cases of subarachnoid hemorrhage occurred in both groups (4). Significantly fewer myocardial infarctions and coronary revascularizations occurred in the rosuvastatin group than in the placebo group. There was no significant difference between the two groups in the number of participants who had new-onset diabetes. Death from cardiovascular causes occurred in 154 participants (2.4%) in the rosuvastatin group and in 171 (2.7%) in the placebo group, and death from noncardiovascular causes occurred in 180 participants (2.8%) in the rosuvastatin group and in 186 (2.9%) in the placebo group. The total number

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			outcomes, new-onset diabetes	of deaths was 334 in the rosuvastatin group and 357 in the placebo group.
Taylor et al.[178] (2011) Statins vs placebo or usual care	SR (14 RCTs) Patients ≥18 years of age with no restrictions on TC, LDL-C or HDL-C levels, population had ≤10% of patients with a previous history of cardiovascular disease	N=34,272 ≥12 months	Primary: All-cause mortality; fatal and nonfatal CHD; cardiovascular disease and stroke events; combined endpoint of fatal and non fatal CHD, cardiovascular disease and stroke Secondary: Change from baseline in TC, revascularization, adverse events, quality of life	Primary: None of the individual trials (eight) showed strong evidence of a reduction in all-cause mortality, but pooled analysis demonstrated that statins were associated with a significant 16% decrease in all-cause mortality (RR, 0.84; 95% CI, 0.79 to 0.96). Four trials demonstrated a significant reduction in the combined endpoint of fatal and nonfatal CHD in favor of statins (RR, 0.72; 95% CI, 0.65 to 0.79). Six trials demonstrated a significant reduction in combined endpoint of fatal and nonfatal cardiovascular disease in favor of statins (RR, 0.74; 95% CI, 0.66 to 0.85). Seven trials demonstrated a significant reduction in stroke events in favor of statins (RR, 0.78; 95% CI, 0.65 to 0.94). Three trials demonstrated a significant reduction in the combined endpoint of fatal and nonfatal CHD, cardiovascular disease and stroke in favor or statins (RR, 0.70; 95% CI, 0.61 to 0.79). Secondary: Five trials demonstrated a significant reduction in revascularization in favor of statins (RR, 0.66; 95% CI, 0.53 to 0.83). Nine and 11 trials reported on TC and LDL-C, demonstrating significant reductions in both with a statin (0.89 mmol/L [95% CI, -1.20 to -0.57] and 0.92 [95% CI, -1.10 to -0.74]). In terms of adverse events, incidence rates indicated no difference between statins and control groups (RR, 0.99; 95% CI, 0.94 to 1.05). There was no reliable data on patient quality of life.
Mora et al.[179] (2010)	MA (5 primary prevention statin RCTs)	N=not reported Duration not	Primary: Cardiovascular disease, all	Primary: Compared to placebo, statin therapy in women significantly reduced cardiovascular disease by about one third in exclusively primary prevention

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Statin therapy vs placebo	Women receiving statin therapy	reported	cause mortality Secondary: Not reported	trials. The summary RR for the three trials was 0.63 (95% CI, 0.49 to 0.82; P<0.001). When trials that included predominately primary prevention were analyzed together with the exclusively primary prevention trials, the summary RR was similar but no significant (0.79; 95% CI, 0.59 to 1.05; P=0.11). When two additional trials were included that did not report sex specific outcomes for women, the summary RR was unchanged (0.82; 95% CI, 0.69 to 0.98; P=0.03). The summary RR for the three exclusively primary prevention trials (n=13,154 women; 216 deaths) that reported sex specific total mortality was 0.78 (95% CI, 0.53 to 1.15; P=0.21). When all trials that reported sex specific mortality outcomes in predominantly or exclusively primary prevention in women were included, the summary RR was similar. Secondary: Not reported
Baigent et al.[180] (2005) Statins (pravastatin 40 mg/day, fluvastatin 40 to 80 mg/day, simvastatin 20 to 40 mg/day, atorvastatin 10 mg/day, lovastatin 20 to 80 mg/day) vs placebo	MA (14 RCTs) Demographics not reported	N=90,056 ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death) in prespecified subgroups; effect on stroke, cancer, and vascular procedures, vascular events	Primary: Statin therapy was associated with a significant 12% reduction in all-cause mortality per 1 mmol/L reduction in LDL-C compared to placebo (RR, 0.88; 95% CI, 0.84 to 0.91; P<0.0001). Statin therapy was associated with a significant 19% reduction in CHD mortality compared to placebo (3.4 vs 4.4%; RR, 0.81; 95% CI, 0.76 to 0.85; P<0.0001). Statin therapy was associated with a nonsignificant 17% reduction in non-CHD mortality compared to placebo (1.2 vs 1.3%; RR, 0.93; 95% CI, 0.83 to 1.03; P value not reported). Secondary: Statin therapy was associated with a significant 17% reduction in vascular mortality compared to placebo (4.7 vs 5.7%; RR, 0.83; 95% CI, 0.79 to 0.87; P<0.0001). Statin therapy was associated with a significant 21% reduction in major vascular events compared to placebo (RR, 0.79; 95% CI, 0.77 to 0.81; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Statin therapy was associated with a significant 26% reduction in nonfatal MI compared to placebo (RR, 0.74; 99% CI, 0.70 to 0.79; P<0.0001). Statin therapy was associated with a significant 23% reduction in any major coronary event compared to placebo (RR, 0.77; 95% CI, 0.74 to 0.80; P<0.0001). Statin therapy was associated with a significant 24% reduction in any coronary revascularization compared to placebo (RR, 0.76; 95% CI, 0.73 to 0.80; P<0.0001). Statin therapy was associated with a significant 21% reduction in any stroke compared to placebo (RR, 0.79; 95% CI, 0.77 to 0.81; P<0.0001). Statin therapy was associated with a nonsignificant increase in the incidence of rhabdomyolysis compared to placebo (P=0.4).
No authors listed.[181] (2008) CTT Collaborators Statins (pravastatin 40 mg/day, fluvastatin 40 to 80 mg/day, simvastatin 20 to 40 mg/day, atorvastatin 10 mg/day, lovastatin 20 to 80 mg/day) vs	MA, subanalysis (14 trials) Demographics not reported	N=90,056 ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality among diabetes and non-diabetes patients Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death), major vascular events among diabetic and non-	Primary: Among patients with diabetes, statins were associated with a significant nine percent reduction in all-cause mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.91; 99% CI, 0.82 to 1.01; P=0.02). Among patients without diabetes, statins were associated with a significant 13% reduction in all-cause mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.87; 99% CI, 0.82 to 0.92; P<0.0001). Secondary: Among patients with diabetes, statins were associated with a significant 13% reduction in vascular mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.87; 99% CI, 0.76 to 1.00; P=0.008) and no effect on nonvascular mortality (RR, 0.97; 99% CI, 0.82 to 1.16; P=0.7). Among patients with diabetes, statins were associated with a significant 21% reduction in major vascular events per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.79; 99% CI, 0.72 to 0.86; P<0.0001). Among patients without diabetes, statins were associated with a significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo			diabetic patients	21% reduction in major vascular events per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.79; 99% CI, 0.76 to 0.82; P<0.0001). Among patients with diabetes, statins were associated with a significant 22% reduction in MI or coronary death (RR, 0.78; 99%CI, 0.69 to 0.87; P<0.0001), 25% reduction in coronary revascularization (RR, 0.75; 99% CI, 0.64 to 0.88; P<0.0001) and 21% reduction in stroke (RR, 0.79; 99% CI, 0.67 to 0.93; P=0.0002) compared to placebo. After five-years of treating 1,000 diabetic patients with statin therapy, 42 patients may be prevented from having a major vascular event (95% CI, 30 to 55; P value not reported). The benefit was greater among patients with diabetes and known vascular disease at baseline.
O'Regan et al.[182] (2008) Statins (atorvastatin 10 to 80 mg/day, simvastatin 20 to 40 mg/day, fluvastatin 40 to 80 mg/day, pravastatin 10 to 40 mg/day, lovastatin 20 to 73 mg/day) vs placebo	MA (41 primary prevention trials, 1 secondary prevention trial) Demographics not reported	N=121,285 Up to 6 years	Primary: All-cause mortality, all-stroke incidence Secondary: Incidence of cardiovascular deaths, non-hemorrhagic cerebrovascular events, hemorrhagic strokes, fatal strokes	Primary: Compared to placebo, statin therapy was associated with a significant reduction in the risk of all-cause mortality (RR, 0.88; 95% CI, 0.83 to 0.93). Compared to placebo, statin therapy was associated with a significant reduction in the risk of strokes (RR, 0.84; 95% CI, 0.79 to 0.91). Secondary: Compared to placebo, statin therapy was associated with a significant reduction in the risk of cardiovascular death (RR, 0.81; 95% CI, 0.74 to 0.90). Compared to placebo, statin therapy was associated with a significant reduction in the risk of nonhemorrhagic cerebrovascular events (RR, 0.81; 95% CI, 0.69 to 0.94). Compared to placebo, statin therapy was associated with a nonsignificant reduction in the risk hemorrhagic strokes (RR, 0.94; 95% CI, 0.68 to 1.30). Compared to placebo, statin therapy was associated with a nonsignificant reduction in the risk of fatal strokes (RR, 0.99; 95% CI, 0.80 to 1.21). A meta-regression analysis determined that every unit increase in LDL-C was associated with a 0.3% increased risk of mortality (RR, 1.003; 95% CI, 1.0005 to 1.006; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Secondary Prevention of Coronary Heart Disease (Single-Entity Agents)				
Bushnell et al.[183] (2006) Statin therapy vs no statin therapy	MA Patients with CHD or vascular disease	N=22,943 90 days	Primary: Incidence of stroke at 90 days, stroke severity, mortality from strokes, differences between sexes Secondary: Not reported	Primary: Patients reporting statin therapy had lower rates of stroke at 90 days of follow up (HR, 0.72; 95% CI, 0.53 to 0.97; P value not reported). Statin therapy was not associated with a significant reduction in stroke mortality (P=0.8). Women had an increased risk of experiencing a severe stroke compared to men (P=0.035). Statin therapy was not associated with a significant reduction in stroke severity among women (P=0.096). Secondary: Not reported
LaRosa et al.[184] (2005) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	DB, MC, PG, RCT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Individual components of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD,	Primary: Compared to 10 mg, 80 mg was associated with a significant 22% reduction in the incidence of the primary endpoint (10.9 vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; P=0.0002). Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of strokes (3.1 vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.96; P=0.021). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events (5.0 vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; P=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% RRR in cerebrovascular events (P=0.002) and a 0.5% RRR in stroke (P=0.041). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of nonfatal MIs (6.2 vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; P=0.004). Compared to 10 mg, 80 mg was associated with a significant reduction in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			all-cause mortality, any cardiovascular event, and any coronary event, side effects	incidence of major coronary events (8.3 vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0019). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events (26.5 vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of hospitalization for heart failure (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). There was no significant difference between the two treatments in the incidence of death from CHD (3.3 vs 2.4%; HR, 0.74; 95% CI, 0.59 to 0.94; P=0.01). There was no significant difference between the two treatments in the incidence of resuscitation after cardiac arrest (0.5%; HR, 0.96; 95% CI, 0.56 to 1.67; P=0.89). There was no significant difference between the two treatments in the incidence of PAD (5.6 vs 5.5%; HR, 0.97; 95% CI, 0.83 to1.15; P=0.76). There was no significant difference between the two treatments in the incidence of death from any cause (5.6 vs 5.7%; HR, 1.01; 95% CI, 0.85 to 1.19; P=0.92). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of treatment-related adverse events (5.8 vs 8.1%; P<0.001). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of ALT and AST elevations greater than three times the upper limit of normal (0.2 vs 1.2%; P<0.001).
Shah et al.[185]	Subanalysis of	N=4,654	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2008) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) with a previous CABG	5 years	First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Safety	A first major cardiovascular event occurred in 11.4% (n=529) of patients with prior CABG and 8.5% (n=453) of those without prior CABG (HR, 1.38; 95% CI, 1.22 to 1.56; P<0.0001). Among post-CABG patients, a primary endpoint event occurred in 9.7 (n=224) vs 13.0% (n=305) of patients receiving 80 and 10 mg/day, resulting in a 27% RR reduction and a 3.3% ARR (HR, 0.73; 95% CI, 0.62 to 0.87; P=0.0004). During follow up, 11.3 (n=262) vs 15.9% (n=371) of patients receiving 80 and 10 mg/day underwent repeat coronary revascularization, either with CABG or percutaneous coronary intervention, resulting in a 30% RR reduction and a 4.6% ARR (HR, 0.70; 95% CI, 0.60 to 0.82; P<0.0001). The combined endpoint of a major cardiovascular event or coronary revascularization occurred in 18.0 (n=417) vs 24.2% (n=566) in patients receiving 80 and 10 mg/day, resulting in a 28% RR reduction and a 6.2% ARR (HR, 0.72; 95% CI, 0.64 to 0.82; P<0.0001). Secondary: In the CABG cohort, discontinuations from therapy due to treatment-related adverse events during the five-years of follow up occurred in 3.8 (n=87) vs 2.7% (n=62) of patients receiving 80 and 10 mg/day (P=0.004). Treatment-related myalgias were reported in 1.3% of patients receiving both treatments, and no post-CABG patient experienced an elevation of CK >10 times the upper limit of normal on two consecutive measurements. Elevated AST and ALT greater than three times the upper limit of normal on consecutive measurements occurred in 1.1 and 0.3% of patients receiving 80 and 10 mg/day (P=0.0003).
Waters et al.[186] (2006) TNT Atorvastatin 10 mg/day vs	Subanalysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization,	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or	Primary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of the primary endpoint (10.9 vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; P=0.0002). Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of strokes (3.1 vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.86; P=0.021).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 80 mg/day	angina with objective evidence of coronary disease)		nonfatal stroke) Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, any coronary event	Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events (5.0 vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; P=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% RR reduction in cerebrovascular events (P=0.002) and a 0.5% RR reduction in stroke (P=0.041). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of nonfatal MIs (6.2 vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; P=0.004). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of major coronary events (8.3 vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0019). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events (26.5 vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). There was no significant difference between the two treatments in the incidence of TIAs (P=0.099). There was no significant difference between the two treatments in the incidence of death from CHD (P=0.087). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of treatment-related adverse events (5.8 vs 8.1%; P<0.001). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of ALT and AST elevations at least three times the upper limit of normal (0.2 vs 1.2%; P<0.001).
Deedwania et	Post hoc analysis	N=5,584	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
al.[187] (2006) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease), stratified by metabolic syndrome	5 years	First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) among patients with metabolic syndrome Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, any coronary event among patients with metabolic syndrome	Compared to 10 mg, 80 mg was associated with a significant 29% reduction in the incidence of the primary endpoint among patient with metabolic syndrome (13.0 vs 9.5%; HR, 0.71; 95% CI, 0.61 to 0.84; P<0.0001). Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events among patients with metabolic syndrome (HR, 0.74; 95% CI, 0.59 to 0.93; P=0.011). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of major coronary events among patients with metabolic syndrome (HR, 0.72; 95% CI, 0.60 to 0.86; P=0.0004). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events among patients with metabolic syndrome (HR, 0.75; 95% CI, 0.67 to 0.83; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events among patients with metabolic syndrome (HR, 0.78; 95% CI, 0.71 to 0.85; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of hospitalization for CHF among patients with metabolic syndrome (HR, 0.73; 95% CI, 0.55 to 0.96; P=0.027). There was no significant difference between the two treatments in the incidence of all-cause mortality among patients with metabolic syndrome (P value not reported).
Shepherd et al.[188] (2006) TNT Atorvastatin 10 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with type 2 diabetes and CHD (either	N=1,501 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation	Primary: Compared to 10 mg, 80 mg was associated with a significant 25% reduction in the incidence of the primary endpoint among patients with diabetes (17.9 vs 13.8%; HR, 0.75; 95% CI, 0.58 to 0.97; P=0.026). Secondary: Significant differences between the treatments in favor of 80 mg/day were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 80 mg/day	previous MI, coronary revascularization, angina with objective evidence of coronary disease)		after cardiac arrest or fatal or nonfatal stroke) among patients with type 2 diabetes Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, any coronary event among patients with type 2 diabetes	observed for the secondary outcomes of time to cerebrovascular event (HR, 0.69; 95% CI, 0.48 to 0.98; P=0.037) and time to cardiovascular event (HR, 0.85; 95% CI, 0.73 to 1.00; P=0.044) There was no significant difference between the two treatments in the incidence of cerebrovascular events among patients with diabetes (P=0.437). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of nonfatal MI among patients with diabetes (HR, 0.79; 95% CI, 0.55 to 1.14; P=0.202). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of fatal and nonfatal stroke among patients with diabetes (HR, 0.67; 95% CI, 0.43 to 1.04; P=0.075). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from CHD among patients with diabetes (HR, 0.74; 95% CI, 0.47 to 1.18; P=0.203). There was no significant difference between the two treatments in the incidence of major coronary events among patients with diabetes (P=0.922). There was no significant difference between the two treatments in the incidence of any coronary events among patients with diabetes (P=0.192). There was no significant difference between the two treatments in the incidence of any cardiovascular events among patients with diabetes (P=0.458). There was no significant difference between the two treatments in the incidence of major cardiovascular events among patients with diabetes (P=0.689). There was no significant difference between the two treatments in the incidence of hospitalization with heart failure among patients with diabetes (P=0.277).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				There was no significant difference between the two treatments in the incidence of all-cause mortality among patients with diabetes (P=0.521). There was no significant difference between the two treatments in the incidence of PAD among patients with diabetes (P=0.789). There was no significant difference between the two treatments in the incidence of treatment-related adverse effects or persistent elevations in liver enzymes (P values not reported).
Wenger et al.[189] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients ≥65 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=3,809 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Individual components of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, and any coronary event, side effects	Primary: Compared to 10 mg, 80 mg was associated with a significant 19% reduction in the incidence of the primary endpoint among patients ≥65 years of age (12.6 vs 10.3%; HR, 0.81; 95% CI, 0.67 to 0.98; P=0.032). Consequently, in treating 35 patients with 80 mg vs 10 mg, one cardiovascular event could be prevented over a five-year period. Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events among patients ≥65 years of age (P=0.010). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of nonfatal MI among patients ≥65 years of age (HR, 0.79; 95% CI, 0.60 to 1.03; P=0.084). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of fatal and nonfatal stroke among patients ≥65 years of age (HR, 0.79; 95% CI, 0.57 to 1.09; P=0.158). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from CHD among patients ≥65 years of age (HR, 0.91; 95% CI, 0.63 to 1.29; P=0.59). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of resuscitated cardiac arrests among patients ≥65 years of age (HR, 1.19; 95% CI, 0.49 to 2.87; P=0.70).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events among patients ≥65 years of age (P<0.001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events among patients ≥65 years of age (P<0.001). Compared to 10 mg, 80 mg was associated with a significant reduction in incidence of hospitalization for heart failure among patients ≥65 years of age (P=0.008). There was no significant difference between the two treatments in the incidence of major coronary events among patients ≥65 years of age (P=0.128). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from cardiovascular causes among patients ≥65 years of age (HR, 0.91; 95% CI, 0.67 to 1.24; P=0.55). Compared to patients receiving 10 mg, more patients receiving 80 mg died from noncardiovascular causes among patients ≥65 years of age (HR, 1.26; 95% CI, 0.93 to 1.70; P=0.129). More patients ≥65 years of age receiving 80 mg experienced treatment-related adverse events compared to patients ≥65 years of age receiving 10 mg (P value not reported).
Khush et al.[190] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence	N=10,001 5 years	Primary: Hospitalization for heart failure among patients with and without a history of heart failure Secondary: Not reported	Primary: Prior history of heart failure is a significant risk factor for hospitalization from heart failure. While 14.1% of patients with heart failure at baseline were hospitalized for heart failure, only 1.9% of patients who did not have heart failure at baseline were hospitalized for heart failure during the trial period (P<0.001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of hospitalization from heart failure among patients with heart failure at baseline (17.3 vs 10.6%; HR, 0.59; 95% CI, 0.4 to 0.80; P=0.008).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	of coronary disease)			Mortality was significantly higher among patients with heart failure compared to patients without heart failure at baseline (15.0 vs 4.9%; P<0.001). Each reduction of 1 mg/dL in LDL-C was associated with a reduction in the risk of hospitalization for heart failure by 0.6% (P=0.007). Secondary: Not reported
LaRosa et al.[191] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease), stratified by LDL-C level	N=9,769 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with LDL-C <64 mg/dL (Quintile 1), 64 to ≤77 mg/dL (Quintile 2), 77 to ≤90 mg/dL (Quintile 3), 90 to ≤106 mg/dL (Quintile 4), and ≥106 mg/dL (Quintile 5) Secondary: Any occurrence of a major coronary event, cerebrovascular	Primary: Patients in the lowest LDL-C Quintiles were associated with the most reduction in the primary endpoint (P<0.0001). Secondary: Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of death from CHD (P<0.01). Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of nonfatal MIs (P<0.0001). Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of stroke (P<0.05). There were no differences in the incidence of all-cause mortality across LDL-C Quintiles (P=0.104). There were no differences in the incidence of cardiovascular mortality across quintiles (P=0.060). There were no differences in the incidence of all-cause mortality across LDL-C Quintiles (P=0.653). There were no differences in the incidence of treatment-related adverse effects across LDL-C Quintiles (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, and any coronary event among patients classified as Quintile 1, 2, 3, 4 or 5 (from above)	
Barter et al.[192] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease), stratified by HDL-C level	N=9,770 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with HDL-C <38 mg/dL (Quintile 1), 38 to 42 mg/dL (Quintile 2), 43 to 47 mg/dL (Quintile 3), 48 to 54 mg/dL (Quintile 4), and ≥55 mg/dL (Quintile 5)	Primary: Patients in the highest HDL-C Quintiles were associated with the greatest reduction in the primary endpoint (P=0.04). Compared to patients in HDL-C Quintile 1, patients classified as HDL-C Quintile 5 had a 25% reduction in risk of a major cardiovascular event (HR, 0.75; 95% CI, 0.60 to 0.95). An increase in 1 mg/dL in HDL-C reduces the risk of major cardiovascular events by 1.1% at three months (P=0.003). Patients with the lowest LDL-C:HDL-C were at a significantly lower risk for major cardiovascular events (P=0.006). Patients with the lowest TC:HDL-C were at a significantly lower risk for major cardiovascular events (P value not reported). Among patients whose LDL-C was <70 mg/dL, those in the highest HDL-C Quintile were at the lowest risk for a major cardiovascular event (P=0.03). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			Secondary: Not reported	
Shepherd et al.[193] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=9,770 5 years	Primary: GFR Secondary: Not reported	Primary: Eighty mg was associated with a significant increase in GFR from baseline over the five-year trial period compared to 10 mg (P<0.0001). Secondary: Not reported
Pitt et al.[194] (1999) AVERT Atorvastatin 80 mg/day vs percutaneous coronary transluminal angioplasty	MC, OL, RCT Adult patients with stable CAD, LDL-C ≥115 mg/dL, TG ≤500 mg/dL, stenosis ≥50% in ≥1 coronary artery and had been recommended for treatment with percutaneous revascularization, asymptomatic or with Canadian Cardiovascular Society Class I or II angina, able to complete ≥4 minutes of a treadmill test or a bicycle exercise	N=341 18 months	Primary: Number of ischemic events and/or need for re-vascularization, angina symptoms, adverse events Secondary: Not reported	Primary: Atorvastatin was associated with a significantly lower incidence of ischemic events compared to revascularization procedure (21 vs 13%; P=0.048). Atorvastatin was associated with a significantly longer time to the first ischemic event compared to revascularization procedure (P=0.03). A significantly smaller proportion of patients receiving atorvastatin had an improvement in the Canadian Cardiovascular Society classification of angina symptoms compared to revascularization procedure (41 vs 54%; P=0.009). Adverse events were similar between the two treatments (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	test without marked ECG changes indicative of ischemia			
Athyros et al.[195] (2002) GREACE Atorvastatin 10 mg/day, titrated up to 80 mg/day vs usual medical care (lifestyle modification and pharmacotherapy, including lipid lowering agents)	RCT Adult patients with established CHD not at LDL-C goal (<100 mg/dL) according to the NCEP criteria	N=1,600 3 years	Primary: Death, nonfatal MI, unstable angina, CHF, revascularization (coronary morbidity), stroke Secondary: Safety	Primary: Compared to usual care, atorvastatin was associated with a significant 51% reduction in the risk for CHD recurrent events or death (24.5 vs 12.0%; P<0.0001). Compared to usual care, atorvastatin was associated with a significant 43% reduction in all-cause mortality (5.0 vs 2.9%; P=0.0021). Compared to usual care, atorvastatin was associated with a significant 47% reduction in the risk of stroke (2.1 vs 1.1%; P=0.034). Compared to usual care, atorvastatin was associated with a significant 47% reduction in the risk of coronary mortality (4.8 vs 2.5%; P=0.0017). Compared to usual care, atorvastatin was associated with a significant 54% reduction in the risk of coronary morbidity (P<0.0001). Atorvastatin was associated with a reduction in TC by 36%, LDL-C by 46%, TG by 31% and non-HDL-C by 44% and an increase in HDL-C by seven percent (P value not reported). Compared to usual care, a greater proportion of patients receiving atorvastatin achieved the NCEP LDL-C goals (3 vs 95%, respectively; P value not reported). Compared to usual care, a greater proportion of patients receiving atorvastatin achieved the NCEP non-HDL-C goals (14 vs 97%, respectively; P value not reported). Secondary: Withdrawals due to adverse effects were similar between the two treatments (0.75 vs 0.40%; P value not reported).
Athyros et al.[196]	Post hoc analysis	N=1,600	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2007) GREACE Atorvastatin 10 mg/day, titrated up to 80 mg/day vs usual medical care (lifestyle modification and pharmacotherapy, including lipid lowering agents)	of GREACE Adult patients with established CHD not at LDL-C goal (<100 mg/dL) according to the NCEP criteria, stratified by the presence of metabolic syndrome	3 years	Vascular events, estimated GFR, serum uric acid level Secondary: Not reported	Among patients with metabolic syndrome, atorvastatin was associated with a significant 57% reduction in the incidence of vascular events compared to usual medical care (12.1 vs 28.0%; RR, 0.43; 95% CI, 0.20 to 0.64; P<0.0001). Among patients without metabolic syndrome, atorvastatin was associated with a significant 41% reduction in the incidence of vascular events compared to usual medical care (RR, 0.59; 95% CI, 0.41 to 0.79; P<0.0001). Atorvastatin was associated with a significant increase in GFR and a reduction in serum uric acid level from baseline (P<0.05), regardless of metabolic syndrome status. Usual medical care was associated with a significant reduction in GFR and an increase in serum uric acid level from baseline (P<0.05), regardless of metabolic syndrome status. Compared to patients without metabolic syndrome, patients with metabolic syndrome experienced a greater increase in GFR with atorvastatin (P=0.02). Secondary: Not reported
Schwartz et al.[197] (2005) MIRACL Atorvastatin 80 mg/day vs placebo Treatment was administered within 96 hours of hospital admission with an ACS.	DB, MC, RCT Patients >18 years of age with unstable angina or non-Q-wave acute MI, with chest pain or discomfort ≥15 minutes that occurred at rest or with minimal exertion within the 24 hour period preceding hospitalization and representing a change from their usual anginal pattern	N=3,086 16 weeks	Primary: A composite endpoint of death, nonfatal acute MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization Secondary: Occurrence of the individual	Primary: Compared to placebo, atorvastatin was associated with a 16% reduction in the risk of a composite endpoint of death, nonfatal acute MI, resuscitated cardiac arrest and recurrent symptomatic myocardial ischemia requiring hospitalization (17.4 vs 14.8%; P=0.048). Secondary: Compared to placebo, atorvastatin was associated with a significant 26% reduction in the risk of a recurrent ischemia requiring hospitalization (RR, 0.74; 95% CI, 0.57 to 0.95; P=0.02). Compared to placebo, atorvastatin was associated with a significant 50% reduction in the risk of a fatal and nonfatal stroke (RR, 0.50; 95% CI, 0.26 to 0.99; P=0.045). There were no significant differences between the two treatments in the incidence of coronary revascularization procedures, worsening heart failure, worsening angina, occurrence of at least one secondary endpoint or occurrence of at least one primary or secondary endpoint (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			components of the primary endpoint, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospitalization but without new objective evidence of ischemia and coronary revascu-larization; time to occurrence of any of the above; percent changes from baseline in lipid levels; safety	Liver transaminase elevation was more common with atorvastatin (2.5 vs 0.6%; P<0.001).
Olsson et al.[198] (2007) MIRACL Atorvastatin 80 mg/day vs placebo	Post hoc analysis of MIRACL Patients ≥65 years of age with unstable angina or non-Q-wave acute MI, with chest pain or discomfort ≥15 minutes duration that occurred at	N=3,086 16 weeks	Primary: A composite endpoint of death, nonfatal acute MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischemia with	Primary: Compared to placebo, atorvastatin was associated with a nonsignificant 14% reduction in the RR of the primary endpoint in patients ≥65 years of age (HR, 0.86; 95% CI, 0.70 to 1.07; ARR, 2.9%; P=0.18). Compared to placebo, atorvastatin was associated with a nonsignificant 22% reduction in the RR of the primary endpoint in patients <65 years of age (HR, 0.78; 95% CI, 0.56 to 1.06; ARR, 2.5%; P=0.11). Secondary: There was no significant difference in any of the secondary endpoints between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Treatment was administered within 96 hours of hospital admission with an ACS.	rest or with minimal exertion within the 24 hour period preceding hospitalization and representing a change from their usual anginal pattern		objective evidence requiring hospitalization among patients ≥65 and <65 years of age Secondary: Occurrence of the individual components of the primary endpoint, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospitalization but without new objective evidence of ischemia, coronary revascu-larization, time to occurrence of any of the above; percent change from baseline in lipid levels among	patients ≥65 and <65 years of age (P>0.05). The frequency of adverse events was similar between the two treatments (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			patients ≥65 and <65 years of age; safety	
Amarenco et al.[199] (2006) SPARCL Atorvastatin 80 mg/day vs placebo	DB, PC, RCT Patients ≥18 years of age who had an ischemic or hemorrhagic stroke or TIA 1 to 6 months before trial entry (patients with a prior hemorrhagic stroke could be included if they were deemed to be at risk for ischemic stroke or CHD) and LDL-C ≥100 to ≤190 mg/dL	N=4,731 Median of 4.9 years	Primary: Time to first occurrence of a nonfatal or fatal stroke Secondary: Occurrence of major cardiovascular events (stroke, cardiac death, nonfatal MI or resuscitated cardiac arrest)	Primary: Patients with a reduction in LDL-C >16% had a significant reduction in stroke compared to those with a reduction <16% (11.0 vs 13.4%; HR, 0.792; 95% CI, 0.671 to 0.935; P=0.0058). Secondary: Patients with a reduction in LDL-C >16% had a significant reduction in major cardiovascular events compared to those with a reduction <16% (13.9 vs 17.3; HR, 0.761; 95% CI, 0.657 to 0.881; P=0.0003).
Amerenco et al.[200] Atorvastatin 80 mg/day vs placebo	Subanalysis of SPARCL to evaluate stroke subtypes Patients ≥18 years of age who had an ischemic or hemorrhagic stroke or TIA 1 to 6 months before trial entry (patients with a prior hemorrhagic stroke could be included if they were	N=4,731 Median of 4.9 years	Primary: Time to first occurrence of a nonfatal or fatal stroke Secondary: Occurrence of major cardiovascular events (stroke, cardiac death, nonfatal MI or resuscitated cardiac arrest), all-cause	Primary: Atorvastatin was similarly effective in reducing the primary endpoint for all entry event stroke subtypes (large vessel, TIA, small vessel and unknown). Although there was no overall heterogeneity between subtypes, the patients with baseline hemorrhagic stroke receiving atorvastatin were qualitatively different and were more than three times more likely to have a recurrent stroke compared to placebo. Secondary: Atorvastatin was similarly effective in reducing the occurrence of major cardiovascular events for all entry event stroke subtypes (large vessel, TIA, small vessel and unknown). Mortality rates were similar across all entry event stroke subtypes. The analyses were also carried out with adjustment for BP, diabetes and ambulatory score at baseline and the results did not differ.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	deemed to be at risk for ischemic stroke or CHD) and LDL-C ≥100 to ≤190 mg/dL		mortality	
Szarek et al.[201] (2020) Atorvastatin 80 mg/day vs placebo	Post hoc analysis of SPARCL Patients ≥18 years of age who had an ischemic or hemorrhagic stroke or TIA 1 to 6 months before trial entry (patients with a prior hemorrhagic stroke could be included if they were deemed to be at risk for ischemic stroke or CHD) and LDL-C ≥100 to ≤190 mg/dL	N=4,731 Median of 4.9 years	Primary: First and subsequent vascular events overall and by territory (cerebrovascular, coronary, or peripheral) Secondary: Not reported	Primary: The placebo group had an estimated 41.2 first and 62.7 total vascular events per 100 participants over six years. There were 164 fewer first and 390 fewer total vascular events in the atorvastatin group (total events hazard ratio, 0.68; 95% CI, 0.60 to 0.77). The total events reduction included 177 fewer cerebrovascular, 170 fewer coronary, and 43 fewer peripheral events. Over six years, an estimated 20 vascular events per 100 participants were avoided with atorvastatin treatment. Secondary: Not reported
Sang et al.[202] (2009) Atorvastatin 10 mg/day vs atorvastatin 10 mg/day and niacin ER	RCT Patients with clinical and angiographic criteria for coronary disease, with ≥50% stenosis of 1 coronary artery with high TC	N=108 12 months (plus a 12 month follow up)	Primary: All-cause mortality, MI, rehospitalization, revascularization with either PCI or CABG Secondary: Mean percent changes from baseline lipid	Primary: At 12 months, clinical events included rehospitalization due to angina pectoris and heart failure attack, respectively, revascularization with PCI and sudden death (7.14%) with atorvastatin. With combination therapy, the clinical events included rehospitalization due to heart failure attack, revascularization after PCI or CABG (5.77%). No significant reduction was observed with combination therapy (OR, 0.78; P=0.052). Secondary: TC, TG, LDL-C and Lp(a) levels decreased significantly with both treatments (P<0.01), with no significant difference between the two during the course of follow up (P>0.05). Apo A increased significantly with both treatments (P<0.01), with a more favorable effect observed with combination therapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			parameters, effects on glucose metabolism, safety	(24.5 vs 40.8%; P<0.01). During the follow up, apo B fell by 5.63 (P<0.05 and 7.35% (P<0.01) with atorvastatin and combination therapy; with no significant difference between the two (P>0.05). During the trial, HDL-C levels increased by 11.67 (P<0.05) and 29.36% (P<0.01) with atorvastatin and combination therapy, with a significant difference favoring combination therapy (P<0.01). Niacin resulted in no significant increase in glucose levels at six or 12 months compared to baseline levels (P>0.05). In the subgroup of diabetic patients (n=28), niacin resulted in a significant increase in glucose levels at six months (P<0.01), and glucose levels increased more significantly at 12 months (P<0.01), but the effect of niacin was not significant in nondiabetic patients (P>0.05). HbA_{1c} levels did not show a significant increase at six months in patient with diabetes, but levels increased significantly at 12 months (P<0.05). Both treatments were generally well tolerated. The most common side effect of niacin therapy was flushing which appeared in four patients receiving combination therapy; however, all patients continued the medication and the flushing disappeared.
Serruys et al.[203] (2002) LIPS Fluvastatin 40 mg BID vs placebo	DB, MC, PC, RCT Patients 18 to 80 years of age with angina or silent ischemia following successful completion of their first PCI, with baseline TC 135 to 270 mg/dL and fasting TG <400 mg/dL	N=1,677 3 to 4 years	Primary: Incidence of major adverse cardiac events (cardiac death, nonfatal MI or a reintervention procedure of CABG or repeat PCI) Secondary: Major adverse cardiac events excluding reintervention procedures (surgical or PCI) occurring	Primary: Major adverse cardiac event-free survival time was significantly longer with fluvastatin compared to placebo (P=0.01). Major adverse cardiac events occurred significantly less frequently with fluvastatin compared to placebo (21.4 vs 26.7%; RR, 0.78; 95% CI, 0.64 to 0.95; P=0.01). During the follow up period, 13 patients (1.5%) receiving fluvastatin compared to 24 patients (2.9%) receiving placebo died from cardiac causes, 30 patients (3.6%) compared to 38 patients (4.6%) had a nonfatal MI and 167patients (19.8%) compared to193 patients (23.2%) underwent CABG or PCI (P values not reported). Secondary: The risk of major adverse cardiac events, excluding reintervention procedures (surgical or PCI), occurring in the first six months of follow up for lesions treated at the index procedure was 33% lower (RR, 0.67; 95% CI, 0.54 to 0.8; P<0.001) with fluvastatin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			in the first six months of follow up for lesions treated at the index procedure, cardiac mortality, combined cardiac mortality and MI, combined all-cause mortality and MI, treatment effects on measured lipid levels, discontinuation rates, tolerability, safety	There was no difference in the reduction of cardiac mortality, combined cardiac mortality and MI and combined all-cause mortality and MI between the two treatments (P=0.07, P=0.07 and P=0.08, respectively). After six weeks, fluvastatin significantly reduced LDL-C by 27% (95% CI, 25 to 29% compared to an 11% reduction with placebo (95% CI, 9 to 13; P<0.001). TG reductions were greater with fluvastatin compared to placebo (22 vs 14%; P value not reported). HDL-C increased by a median of 22% with both treatments (P value not reported). Discontinuation rates due to adverse events were 21.2 and 24.0% with fluvastatin and placebo. Death rates due to noncardiac causes were 2.7 and 3.0% with fluvastatin and placebo. There were three reported cases of elevations in CK ≥10 times the upper limit of normal with placebo. There were 10 patients receiving fluvastatin and three patients receiving placebo who had elevations of at least three times the upper limit of normal level in AST or ALT on two consecutive occasions. Cancers were reported in 46 and 49 patients receiving fluvastatin and placebo (P values not reported).
Liem et al.[204] (2002) FLORIDA Fluvastatin 80 mg/day vs placebo	DB, PC, PG, RCT Adult patients with an acute MI and TC <6.5 mmol/L, new or markedly increased chest pain lasting >30 minutes or a new pathological Q wave ≥0.04 seconds duration, or ≥25% of the corresponding R	N=540 1 year	Primary: Presence of either ischemia on ambulatory ECG monitoring at 12 months or the occurrence of a major clinical event Secondary: Six week and 12 month	Primary: After 12 months, fluvastatin did not significantly affect ischemia on ambulatory ECG (P=0.67), nor the occurrence of any major clinical event (P=0.24) when compared to placebo. Secondary: In patients with ischemia at baseline, 29 and 38% receiving fluvastatin and placebo were ischemic on the ambulatory ECG at six weeks and 27 and 21% were again positive for ischemia at 12 months (P value not reported). The six week and 12 month ischemic burden was lowered by 6.1 and 7.7%, respectively, with fluvastatin and by 10.5 and 13.0%, respectively, with placebo (P=0.81 and P=0.43, respectively between treatment groups).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	wave amplitude, both in ≥2 contiguous leads		incidence of ischemia on the ambulatory ECG, six week and 12 month change in ischemic burden, 12 month change in lipid profile, safety and tolerability	After 12 months, fluvastatin lowered LDL-C by 21% compared to an increase of nine percent with placebo (P<0.001). There were 62 and 68 patients receiving fluvastatin and placebo who had at least one major clinical event (P=0.764). All-cause mortality was 2.6 and 4.0% with fluvastatin and placebo (P value not reported).
Sacks et al.[205] (1996) CARE Pravastatin 40 mg QD vs placebo	DB, MC, RCT Adult post MI patients with TC <240 mg/dL, LDL-C 115 to 174 mg/dL, TG <350 mg/dL, glucose ≤220 mg/dL, left ventricular ejection fractions ≥25 percent and no symptomatic CHF	N=4,159 5 years	Primary: Death from CHD (including fatal MI, either definite or probable, sudden death, death during a coronary intervention and death from other coronary causes) or a symptomatic nonfatal MI confirmed by serum CK Secondary: Not reported	Primary: When compared to placebo, there was a significant 24% lower incidence of the primary endpoint with pravastatin (13.2 vs 10.2%; 95% CI, 9 to 36; P=0.003). Pravastatin was associated with a significant 23% risk reduction in nonfatal MIs compared to placebo (P=0.02). Pravastatin was associated with a nonsignificant 37% reduction in the rate of fatal MIs (95% CI, -5 to 62; P=0.07) and a nonsignificant 25% reduction in the rate of total MIs (95% CI, 8 to 39; P=0.06) compared to placebo. Secondary: Not reported
No authors listed.[206] (1998) LIPID	DB, MC, PC Patients 31 to 75 years of age who were post MI or	N=9,014 6.1 years	Primary: Death from CHD Secondary:	Primary: Death from CHD occurred in 6.4 and 8.3% of patients receiving pravastatin and placebo (RRR, 24%; 95% CI, 12 to 35; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Pravastatin 40 mg QD vs placebo	who had a hospital discharge diagnosis of unstable angina between 3 and 36 months before trial entry		Incidence of MI and stroke, rate of CABG surgery	Pravastatin was associated with a significant 29% reduction in the incidence of MI compared to placebo (7.4 vs 10.3%; P<0.001). Pravastatin was associated with a significant 19% reduction in the incidence of stroke compared to placebo (3.7 vs 4.5%; P=0.048). Pravastatin was associated with a significant 22% reduction in the risk of CABG surgery compared to placebo (9.2 vs 11.6%; P<0.001). Pravastatin was associated with a significant 19% reduction in the risk of coronary angioplasty compared to placebo (4.7 vs 5.6%; P=0.024). Pravastatin was associated with a significant 12% reduction in the risk of unstable angina compared to placebo (22.3 vs 24.6%; P=0.005).
Shepherd et al.[207] (2002) PROSPER Pravastatin 40 mg QD vs placebo	DB, MC, PC, RCT Patients 70 to 82 years of age with pre-existing vascular disease (coronary, cerebral or peripheral) or at an increased risk of such disease due to risk factors (smoking, HTN, or diabetes) with TC 4 to 9 mmol/L and TG <6 mmol/L	N=5,804 Mean, 3.2 years (range, 2.8 to 4.0 years)	Primary: Combined endpoint of definite or suspect death from CHD, nonfatal MI and fatal or nonfatal stroke Secondary: Examination of coronary and cerebrovascular components separately, assessment of cognitive function, adverse events, cancer	Primary: Pravastatin was associated with a significant 15% reduction in the risk of the primary endpoint compared to placebo (14.1 vs 16.2%; HR, 0.85; 95% CI, 0.74 to 0.97; P=0.014). Secondary: When the primary endpoint was separated into coronary and cerebrovascular components, the authors noted a 19% reduction in coronary events with pravastatin, but no apparent effect on cerebrovascular events (P value not reported). Pravastatin was associated with a significant 19% reduction in the risk of CHD death or nonfatal MI compared to placebo (10.1 vs 12.2%; HR, 0.81; 95% CI, 0.69 to 0.94; P=0.006). When examining the rates of fatal or nonfatal stroke, there was no significant difference between the two treatments (HR, 1.03; 95% CI, 0.81 to 1.31; P=0.81). There was no significant difference in cognitive function between the two treatments (P>0.05). The rate of serious adverse events reported was similar between the two

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				treatments (56 vs 55%, respectively; P value not reported). There were no patients with either treatment reported rhabdomyolysis or CK concentrations >10 times the upper limit of normal (P value not reported). There were no significant differences in the rates of cancer development between the two treatments (P>0.05).
Lloyd et al.[208] (2013) PROSPER Pravastatin 40 mg QD vs placebo	FU Patients enrolled in the PROSPER trial	N=5,804 (5,188 were followed long-term) Mean follow-up of 8.2 years	Primary: All-cause mortality, coronary, stroke, cancer and non-CV mortality	Primary: There was no evidence of any effect on all-cause mortality or on non-CV or CV mortality. During the trial and post-trial there was a numerical excess of stroke deaths in the pravastatin arm; however, this difference did not reach statistical significance. There was a reduction in CHD mortality over the entire period of follow-up (HR 0.80, 95% CI, 0.68 to 0.95; P=0.0091). A suggestion of an increased risk of incident cancer during the trial period (HR, 1.23; 95% CI, 1.01 to 1.49; P=0.038) was not replicated in the post-trial period (HR, 1.08; 95% CI, 0.96 to 1.21; P=0.22).
Thompson et al.[209] (2004) PACT Pravastatin 20 to 40 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 85 years of age with <24 hours onset of symptoms and diagnosis of acute MI or unstable angina pectoris	N=3,408 4 weeks	Primary: Composite of death from any cause, acute MI or readmission to hospital with unstable angina pectoris during the first month following randomization Secondary: Incidence of individual causes of death, acute MI other than the index event, readmission for angina in the	Primary: Pravastatin 40 mg was associated with a nonsignificant 6.4% reduction in the risk of the primary endpoint compared to placebo (P=0.48). Secondary: There were no significant differences in the frequency of individual components of the primary endpoint in the 30 days after randomization between the two treatments (P>0.05). The frequency of adverse events did not differ between the two treatments (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			first month, urgent revascularization procedure, other nonfatal cardiovascular events; adverse events	
Asselbergs et al.[210] (2004) Pravastatin 40 mg QD and fosinopril 20 mg QD vs placebo	DB, PC, RCT Patients aged 28-75 years with persistent micro-albuminuria, BP <160/100 mm Hg (not on antihypertensive medications), TC level <8.0 mmol/L, or <5.0 mmol/L in case of previous MI, and no use of lipid-lowering medication	N=864 46 months	Primary: Combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity (nonfatal or myocardial ischemia, heart failure, peripheral vascular disease and/or cerebrovascular accident) Secondary: Not reported	Primary: Pravastatin therapy was associated with a 13% reduction in the risk of the primary end point compared to placebo (4.8 vs 5.6%; P=0.649). The incidence of non-cardiovascular mortality was 2.1% in the pravastatin group compared to 1.9% in the placebo group. Secondary: Not reported
Sato et al.[211] (2008) OACIS-LIPID Pravastatin 10 mg QD vs	MC, OL, RCT Patients with acute MI and mild to moderate hyperlipidemia (TC 200 to 250 mg/dL and TG	N=353 9 months	Primary: Composite end point of death, nonfatal MI, unstable angina, re-vascularization and non-fatal	Primary: The composite end point occurred in 17.9% of patients in the pravastatin group compared to 31.4% of patients in the non-pravastatin group (HR, 0.56; 95% CI, 0.36 to 0.87; P<0.006). There were no significant differences in the risk of death (P=0.643), nonfatal MI (P=0.622), unstable angina (P=0.985), or nonfatal stroke (P=0.252) between the pravastatin group and non-pravastatin group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
no pravastatin	≤300 mg/dL)		stroke, and rehospitalization because of other cardiovascular diseases Secondary: Not reported	There was a lower risk of revascularization in the pravastatin group compared to the non-pravastatin group (12.7 vs 20.6%, P=0.049). Secondary: Not reported
Tavazzi et al.[212] (2008) GISSI-HF Rosuvastatin 10 mg QD vs placebo	RCT, DB, MC, PC Patients ≥18 years of age with symptomatic heart failure (NYHA class II to IV)	N=4,631 Median 3.9 years	Primary: Time to death, and time to death or admission to hospital for cardiovascular reasons Secondary: Cardiovascular mortality, cardiovascular mortality or admission for any reason, sudden cardiac death, admission for any reason, admission for cardiovascular reasons, admission for heart failure, MI, and stroke	Primary: At the end of the follow-up period, 29% of patients in the rosuvastatin group died from any cause compared to 28% of patients in the placebo group (HR, 1.00; 97% CI, 0.898 to 1.122; P=0.943). The composite of all-cause death or admission to hospital for cardiovascular reasons occurred in 57% of patients in the rosuvastatin group compared to 56% of patients in the placebo group (HR, 1.01; 99% CI, 0.908 to 1.112; P=0.903). Secondary: There was no difference in cardiovascular mortality (P=0.804), first hospital admission for any, cardiovascular, or heart failure cause (P=0.962, P=0.613, and P=0.987, respectively), or the combined outcome measure of cardiovascular death or admission to hospital for any cause (P=0.409) sudden cardiac death (P=0.221), MI (P=0.459), and stroke (P=0.174) with rosuvastatin compared to placebo.
Rossebø et al.[213]	DB, MC, RCT	N=1,873	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2008) SEAS Simvastatin 40 mg QD and ezetimibe 10 mg QD vs placebo Open-label lipid-lowering therapy, which included up to 40 mg of simvastatin or an equipotent dose of another lipid-lowering drug, could be administered in addition to the study drug at the discretion of each treating physician	Patients 45 to 85 years of age who had asymptomatic, mild-to-moderate aortic valve stenosis with a peak aortic-jet velocity of 2.5 to 4 m per second	52.2 months (median duration)	Composite of major cardiovascular events (death from cardiovascular causes, aortic-valve replacement, CHF as a result of progression of aortic-valve stenosis, nonfatal MI, hospitalization for unstable angina, CABG, PCI, non-hemorrhagic stroke) Secondary: Aortic-valve events, progression of aortic stenosis, safety	The composite of major cardiovascular events occurred in 35.3% of patients in the simvastatin plus ezetimibe group and in 38.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.83 to 1.12; P=0.59). Secondary: There was no significant difference between the treatments in aortic-valve-related events (HR, 0.97; 95% CI, 0.83 to 1.14; P=0.73). Aortic-valve replacement occurred in 28.3% of patients in the simvastatin plus ezetimibe group and in 29.9% of patients in the placebo group (HR, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Ischemic cardiovascular events occurred in 15.7% of patients in the simvastatin plus ezetimibe group compared to 20.1% of patients in the placebo group (HR, 0.78; 95% CI, 0.63 to 0.97; P=0.02). A total of 7.3% of patients in the simvastatin plus ezetimibe group required CABG compared to 10.8% of patients in the placebo group (HR, 0.68; 95% CI, 0.50 to 0.93; P=0.02). There was no significant difference in the progression of aortic stenosis between the treatment groups. The mean peak aortic jet velocity was 3.71 m per second in the placebo group compared to 3.69 m per second in the simvastatin plus ezetimibe group at the end of the study (95% CI, -0.06 to 0.05; P=0.83). The mean pressure gradient increased to 34.4 mm Hg in the placebo group compared to 34.0±15.1 mm Hg in the simvastatin plus ezetimibe group at the end of the study. There was no significant difference in the aortic-valve area between the treatment groups. There was no significant difference in overall mortality among the treatment groups (P=0.80). The composite outcome of death from cardiovascular causes and the individual components of this composite outcome did not differ significantly between the two groups (P=0.34). There was a significant increase in the number of patients with elevated liver

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				enzyme levels in the simvastatin plus ezetimibe group. There was also a higher incidence of cancer in the simvastatin plus ezetimibe group (11.1%) compared to placebo (7.5%; P=0.01).
No authors listed.[214] (1994) 4S Simvastatin 10 mg/day, titrated up to 40 mg/day vs placebo	DB, PC, RCT Patients 35 to 70 years of age with CHD, a history of angina pectoris or previous MI, TC 212 to 309 mg/dL and TG <221 mg/dL on a lipid-lowering diet	N=4,444 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal acute MI, resuscitated cardiac arrest and definite silent MI)	Primary: Simvastatin was associated with a 30% reduction in all-cause mortality compared to placebo (8 vs 12%; RR, 0.70; 95% CI, 0.58 to 0.85; P=0.0003). Secondary: Overall, patients receiving placebo experienced at least one secondary event compared to patients receiving simvastatin (28 vs 19%, respectively; P value not reported). There were 189 (8.5%) coronary deaths with placebo compared to 111 (5.0%) coronary deaths with simvastatin (RR, 0.58; 95% CI, 0.46 to 0.73; P value not reported). There were 270 (12.1%) definite acute MI with placebo compared to 164 (7.4%) definite acute MI with simvastatin. There were 418 (18.8%) definite or probable acute MI with placebo compared to 279 (12.6%) definite or probable acute MI with simvastatin. There were 110 (4.9%) silent MIs with placebo compared to 88 (4.0%) silent MIs with simvastatin. There was one patient receiving simvastatin who experienced resuscitated cardiac arrest. (P values not reported). Additionally, a cerebrovascular event occurred in 95 (4.3%) patients with placebo compared to 61 (2.7%) patients with simvastatin (RR, 95% CI; P value not reported).
Chonchol et al.[215] 4S (2007) Simvastatin 10 mg/day, titrated up to 40 mg/day vs placebo	Subanalysis of 4S Patients 35 to 70 years of age with CHD, a history of angina pectoris or previous MI, TC 212 to 309 mg/dL and TG <221 mg/dL on a lipid-lowering diet, stratified by estimated GFR of ≥75 or <75	N=4,420 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal acute MI, resuscitated	Primary: Simvastatin was associated with a significant reduction in all-cause mortality among patients with chronic renal insufficiency (HR, 0.70; 95% CI, 0.55 to 0.91; P value not reported). Secondary: Simvastatin was associated with a significant reduction in the incidence of major coronary events among patients with chronic renal insufficiency (HR, 0.68; 95% CI, 0.57 to 0.80; P value not reported). Simvastatin was associated with a significant reduction in the incidence of CHD deaths or nonfatal MIs among patients with chronic renal insufficiency (HR, 0.66; 95% CI, 0.55 to 0.79; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	mL/min/1.73 m^2		cardiac arrest and definite silent MI)	Simvastatin was associated with a significant reduction in the incidence of coronary revascularization among patients with chronic renal insufficiency (HR, 0.63; 95% CI, 0.51 to 0.79; P value not reported). Simvastatin was not associated with a significant reduction in the incidence of stroke among patients with chronic renal insufficiency (HR, 0.86; 95% CI, 0.54 to 1.36; P value not reported).
No authors listed.[216] (2003) MRC/BHF (HPS) Simvastatin 40 mg QD vs placebo	DB, MC, PC, RCT Patients 40 to 80 years of age with a history of CHD, PAD, cerebrovascular disease, diabetes or treated HTN (if also male and ≥65 years of age) with TC ≥135 mg/dL	N=20,536 5 years	Primary: All-cause mortality and CHD death events Secondary: Noncoronary causes of death, major coronary events (nonfatal MI or CHD death), stroke, revascularization, major vascular events (nonfatal MI, CHD death, stroke or revascular-ization), cancer	Primary: During the trial, 12.9 (1,328/10,269) vs 14.7% (1,507/10,267) of patients receiving simvastatin and placebo died (P=0.0003). The effect of simvastatin on all-cause mortality was mainly due to the definite 17% (SE, 4; 95% CI, 9 to 25) proportional reduction in the death rate from vascular causes (7.6 vs 9.1%; P<0.0001), which consists of a highly significant 18% (SE, 5) reduction in the coronary death rate (5.7 vs 6.9%; P=0.0005) and a nonsignificant 16% (SE, 9) reduction in the death rate from other vascular causes (1.9 vs 2.2%; P=0.07). There were no differences in all nonvascular deaths (5.3 vs 5.6%; P=0.4) or in any of the prespecified categories of nonvascular deaths (renal, hepatic and trauma). Secondary: Simvastatin was associated with a significant 38% (SE, 5; 95% CI, 30 to 46) proportional reduction in the incidence rate of first nonfatal MI (3.5 vs 5.6%; P<0.0001). For the endpoint of major coronary events, there was a significant 27% (SE, 4; 95% CI, 21 to 33) proportion reduction in the incidence rate of combined first nonfatal MI or coronary death (8.7 vs 11.8%; P<0.0001). Overall, simvastatin was associated with a significant 25% (SE, 5; 95% CI, 15 to 34) proportional reduction in the incidence rate of fist stroke (4.3 vs 5.7%; P<0.0001). This was due to mainly to a significant 30% (SE, 6; 95% CI, 19 to 40) proportional reduction in the incidence rate of strokes attributed to ischemia (2.8 vs 4.0%; P<0.0001), with no apparent difference in strokes attributed to hemorrhage (0.5 vs 0.5%; P=0.8). Overall, simvastatin was associated with a significant 24% (SE, 4; 95% CI, 17 to 30) proportional reduction in the incidence rate of first revascularization procedure (9.1 vs 11.7%; P<0.0001). Specifically, simvastatin was associated with a significant 30% (SE, 5; 95% CI, 22 to 38) proportional reduction in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				incidence rate of coronary revascularization (5.0 vs 7.1%; P<0.0001). Similar results were observed for noncoronary revascularization (4.4 vs 5.2%; P=0.006). When the data for major coronary events (first nonfatal MI or coronary death), stroke and revascularization are combined for the endpoint of major vascular events, simvastatin was associated with a significant 24% (SE, 3; 95% CI, 19 to 28) proportional reduction in the event rate (19.8 vs 25.2%; P<0.001). New primary cancers were diagnosed in 7.9 and 7.9% of patients receiving simvastatin and placebo (rate ratio, 1.00; 95% CI, 0.91 to 1.11). These cases were associated with death in 3.5 vs 3.4% of patients (rate ratio, 1.03; 95% CI, 0.89 to 1.19). There were also no differences in the incidence of cancers in any particular body system.
Collins et al.[217] (2007) MRC/BHF (HPS) Simvastatin 40 mg QD vs placebo	DB, MC, PC, RCT Patients 40 to 80 years of age with a history of CHD, PAD, cerebrovascular disease, diabetes or treated HTN (if also male and ≥65 years of age) with TC ≥135 mg/dL	N=20,536 (5,963 diabetics and 14,573 patients with occlusive arterial disease without diabetes) 5 years	Primary: Incidence of first nonfatal MI or coronary death; fatal or nonfatal stroke; revascular-ization procedures; first incidence of major coronary events, strokes and revascular-izations Secondary: Not reported	Primary: Simvastatin was associated with a significant 27% reduction in the incidence of first nonfatal MI or coronary death compared to placebo (95% CI, 21 to 33; P<0.0001). Among diabetic patients, simvastatin was associated with a significant 27% reduction in the incidence of first nonfatal MI or coronary death compared to placebo (95% CI, 19 to 34; P<0.0001). Simvastatin was associated with a significant 25% reduction in the incidence of first nonfatal or fatal strokes compared to placebo (95% CI, 15 to 34; P<0.0001). Simvastatin was associated with a significant 26% reduction in the incidence of fatal strokes compared to placebo (95% CI, 14 to 36; P=0.0002). Among diabetic patients, simvastatin was associated with a significant 24% reduction in the incidence of fatal strokes compared to placebo (95% CI, 6 to 39; P=0.01). Simvastatin was associated with a significant 24% proportional reduction in the incidence of first revascularization compared to placebo (95% CI, 17 to 30; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Among diabetic patients, simvastatin was associated with a significant 17% reduction in the incidence of first revascularization procedure compared to placebo (95% CI, 3 to 30; P=0.02). Simvastatin was associated with a significant 24% reduction in the first incidence of major coronary events, strokes and revascularizations compared to placebo (95% CI, 19 to 28; P<0.0001). Among diabetic patients, simvastatin was associated with a significant 22% reduction in the incidence of first incidence of major coronary events, strokes and revascularizations compared to placebo (95% CI, 13 to 30; P<0.0001). Secondary: Not reported
de Lemos et al.[218] (2004) A to Z trial Simvastatin 40 mg/day for 1 month, titrated up to 80 mg/day (intensive therapy) vs placebo for 4 months, followed by simvastatin 20 mg/day (delayed initiation of a less intensive therapy)	DB, MC, PC Adult patients with either non-ST-elevation ACS or STEMI	N=4,497 2 years	Primary: Composite of cardiovascular death, nonfatal MI, readmission for ACS (requiring new ECG changes or cardiac marker elevation) and stroke Secondary: Individual components of the primary endpoint, re-vascularization due to documented ischemia, all-	Primary: Simvastatin 80 mg was associated with a nonsignificant reduction in the risk of the primary endpoint compared to simvastatin 20 mg (14.4 vs 16.7%; HR, 0.89; 95% CI, 0.76 to 1.04; P=0.14). Secondary: Simvastatin 80 mg was associated with a significant reduction in the risk of cardiovascular death compared to simvastatin 20 mg (HR, 0.75; 95% CI, 0.57 to 1.00; P=0.05). There was no significant difference between the two treatments in the secondary endpoints of MI, readmission for ACS, revascularization due to documented ischemia or stroke (P>0.05 for all). Simvastatin 80 mg was associated with a significant reduction in the risk of new onset CHF compared to simvastatin 20 mg (3.7 vs 5.0%; HR, 0.72; 95% CI, 0.53 to 0.98; P=0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			cause mortality, new-onset CHF (requiring admission or initiation of heart failure medications), cardiovascular Re-hospitalization	
No authors listed.[219] (2007) Simvastatin 40 mg QD vs placebo	DB, MC, RCT Patients 40 to 80 years of age with a history of CHD, PAD, cerebrovascular disease, diabetes or treated HTN (if also male and ≥65 years of age) with TC ≥135 mg/dL	N=20,536 5 years	Primary: The first major coronary event (nonfatal MI or coronary death), first major vascular event (major coronary event, stroke or revascular-ization) Secondary: Not reported	Primary: In the overall population, simvastatin was associated with a significant 24% reduction in the first incidence of a major vascular event compared to placebo (19.8 vs 25.2%; P<0.0001). Among patients with baseline PAD, simvastatin was associated with a significant 22% reduction in the first incidence of a major vascular event compared to placebo (26.4 vs 32.7%; P<0.0001). Among patients without baseline PAD, simvastatin was associated with a significant 25% reduction in the first occurrence of a major vascular event compared to placebo (16.5 vs 21.5%; P<0.0001). The difference in the reduction of the risk of major vascular events with statin therapy between the PAD and non-PAD groups was not significant (P=0.05). In the overall population, simvastatin was associated with a significant 27% reduction in the first incidence of a major coronary event compared to placebo (8.7 vs 11.8%; P<0.0001). Among patients with baseline PAD, simvastatin was associated with a significant reduction in the first incidence a major coronary event compared to placebo (10.9 vs 13.8%; P<0.0001). Among patients without baseline PAD, simvastatin was associated with a significant reduction in the first incidence of a major coronary event compared to placebo (7.7 vs 10.8%; P<0.0001). The difference in the reduction of the risk of major coronary events with statin therapy between the PAD and non- PAD groups was not significant (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				In the overall population, simvastatin was associated with a significant 25% reduction in the first incidence of stroke compared to placebo (4.3 vs 5.7%; P<0.0001). Among patients with baseline PAD, simvastatin was associated with a significant reduction in the first incidence of stroke compared to placebo (5.3 vs 7.2%; P<0.0001). Among patients without baseline PAD, simvastatin was associated with a significant reduction in the first incidence of stroke compared to placebo (3.8 vs 5.0%; P<0.0001). The difference in the reduction of the risk of stroke with statin therapy between the PAD and non-PAD groups was not significant (P=0.07). In the overall population, simvastatin was associated with a significant 24% reduction in the first incidence of revascularization compared to placebo (9.1 vs 11.7%; P<0.0001). Among patients with baseline PAD, simvastatin was associated with a significant reduction in the first incidence of revascularization compared to placebo (13.8 vs 17.9%; P<0.0001). Among patients without baseline PAD, simvastatin was associated with a significant reduction in the first incidence of revascularization compared to placebo (6.9 vs 8.7%; P<0.0001). The difference in the reduction of the risk of revascularization with statin therapy between the PAD and non- PAD groups was not significant (P=0.07). In the overall population, simvastatin was associated with a significant 16% reduction in the risk of first incidence of a peripheral vascular event compared to placebo (4.7 vs 5.5%; P=0.006). This risk reduction was independent of baseline LDL-C, age, diabetes or coronary disease (P values not reported). Secondary: Not reported
Pauriah et al.[220] (2014) Simvastatin monotherapy vs	OS, RETRO Patients who had survived 30 days after their first acute MI, had not received prior	N=9,597 Mean follow-up of 3.2 years	Primary: Mortality, lipid levels Secondary: Not reported	Primary: The adjusted HR for the high-potency statin group was 0.72 (95% CI, 0.59 to 0.88; P<0.001), and for the ezetimibe/statin combination group, the adjusted HR was 0.96 (95% CI, 0.64 to 1.43; P<0.85). In the subgroup analysis of 2787 patients with complete data for GFR, cholesterol, and blood pressure, the HR for ezetimibe use and high-potency statin use were 1.03 (95% CI, 0.47 to 2.23; P=0.943) and 0.79 (95% CI, 0.55 to 1.131; P=0.19), respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
high-potency statin group (patients who started on simvastatin and switched to atorvastatin or rosuvastatin) vs ezetimibe/statin combination group	statin or ezetimibe therapy, and were started on a statin within 30 days of acute MI			There was a decrease in total cholesterol and LDL-C in all three groups with significantly greater percentage decrease in these measures in the high-potency statin group and the ezetimibe/statin combination group compared with the simvastatin monotherapy group. Because of higher baseline total cholesterol levels, the best achieved total cholesterol levels were not lower in the high-potency statin and ezetimibe/statin combination groups. Secondary: Not reported
Briel et al.[221] (2006) Statins (pravastatin 10 to 40 mg, fluvastatin 80 mg, atorvastatin 20 to 80 mg, simvastatin 40 to 80 mg) vs placebo	MA (12 PC, RCTs) Patients with ACS (MI or unstable angina), started on statin therapy within 14 days of ACS and with a follow up ≥30 days	N=13,024 ≥30 days	Primary: Composite endpoint of nonfatal MI, nonfatal stroke and total death Secondary: Total death, total MI, total stroke, cardiovascular death, fatal and nonfatal MI, revascularization procedures (CABG surgery, angioplasty) and unstable angina (recurrent	Primary: At either month one or four follow up, there was no significant difference in the primary endpoint between statin therapy and placebo (P=0.39 and P=0.30, respectively). Secondary: At either month one or four of follow up, there was no significant difference in any of the secondary endpoints (except for unstable angina) between statin therapy and placebo (P values not reported). After four months of therapy, statin therapy was associated with a significant moderate reduction in the incidence of unstable angina compared to placebo (P=0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			myocardial ischemia requiring emergency hospitalization)	
Mood et al.[222] (2007) Statins (atorvastatin 20 to 40 mg/day, pravastatin 40 mg/day, fluvastatin 40 mg BID) vs placebo or usual care	MA (6 RCTs) Therapy was initiated around the time of a PCI	N=3,941 up to 45 months	Primary: Incidence of MI Secondary: All-cause mortality, cardiovascular mortality, surgical or percutaneous re-vascularization, stroke	Primary: Compared to placebo or usual care, statin therapy was associated with a significant 43% reduction in the risk for MI (5.2 vs 3.0%; OR, 0.57; 95% CI, 0.42 to 0.78; P<0.0001). Secondary: Compared to placebo or usual care, statin therapy was associated with a nonsignificant 26% reduction in all-cause mortality (3.0 vs 2.3%; OR, 0.74; 95% CI, 0.5 to 1.1; P=0.14). Compared to placebo or usual care, statin therapy was associated with a nonsignificant 42% reduction in cardiovascular mortality (1.20 vs 0.71%; OR, 0.58; 95% CI, 0.30 to 1.11; P=0.10). Compared to placebo or usual care, statin therapy was associated with a nonsignificant 11% reduction in the incidence of repeat surgical or percutaneous revascularization (21.9 vs 19.6%; OR, 0.89; 95% CI, 0.78 to 1.02; P=0.098). The incidence of stroke was nonsignificantly higher with statin therapy compared to placebo or usual care (0.40 vs 0.08%; OR, 3.00; 95% CI, 0.60 to 14.77; P=0.18).
Afilalo et al.[223] (2008) Moderate statin therapy (pravastatin 40 mg/day, fluvastatin 80 mg/day, simvastatin 20 to	MA (9 RCTs) Patients ≥50 years of age with CHD	N=19,569 (9 studies) ≥6 months	Primary: All-cause mortality, CHD mortality, stroke, re-vascularization, nonfatal MI Secondary: Not reported	Primary: Statin therapy was associated with a lower rate of all-cause mortality compared to placebo (15.6 vs 18.7%; RR, 0.78; 95% CI, 0.65 to 0.89; P value not reported). Statin therapy was associated with a significant reduction in the risk of CHD mortality by 30% (RR, 0.70; 95% CI, 0.53 to 0.83), nonfatal MI by 26% (RR, 0.74; 95% CI, 0.60 to 0.89), revascularization by 30% (RR, 0.70; 95% CI, 0.53 to 0.83) and stroke by 25% (RR, 0.75; 95% CI, 0.56 to 0.94).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
40 mg/day) vs placebo				The calculated NNT with statin therapy to save one life was 28 (95% CI, 15 to 56). Secondary: Not reported
Hulten et al.[224] (2006) Intensive statin therapy (pravastatin 40 mg/day, fluvastatin 80 mg/day, simvastatin 80 mg/day, atorvastatin 20 mg/day, atorvastatin 80 mg daily) vs placebo or lower dosed statin therapy	MA (13 RCTs) Adult patients initiated on intensive statin therapy or control within 14 days of hospitalization for ACS	N=17,963 Up to 2 years of follow up	Primary: Composite of death, recurrent ischemia and recurrent MI; death and cardiovascular events; cardiovascular death; ischemia; MI; LDL-C reduction; safety Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with a significantly lower rate of mortality and cardiovascular events over 24 months of follow up (HR, 0.81; 95% CI, 0.77 to 0.87; P<0.001). In patients with recent ACS, intensive statin therapy was associated with a lower risk of overall cardiovascular events over 24 months of follow up (HR, 0.84; 95% CI, 0.76 to 0.94; P value not reported). In patients with recent ACS, intensive statin therapy was associated with lower cardiovascular mortality over 24 months of follow up (HR, 0.76; 95% CI, 0.66 to 0.87). In patients with recent ACS, intensive statin therapy was associated with lower ischemia over 24 months of follow up (HR, 0.68; 95% CI, 0.50 to 0.92). In patients with recent ACS, intensive statin therapy was not associated with a lower incidence of MIs over 24 months of follow up (HR, 0.89; 95% CI, 0.60 to 1.33). Intensive statin therapy was associated with a significantly greater reduction in LDL-C compared to controls (P<0.001). Adverse effects were similar between the two treatments (P value not reported). Secondary: Not reported
Cannon et al.[225] (2004) PROVE IT-TIMI 22	DB, DD, MC, RCT Patients ≥18 years of age in stable	N=4,162 Up to 3 years (mean 2 years)	Primary: Rates of composite death from any	Primary: The rates of composite death from any cause, MI, unstable angina requiring hospitalization, revascularization and stroke at two years were 26.3 and 22.4% with pravastatin and atorvastatin, representing a 16% reduction in the HR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL		cause, MI, documented unstable angina requiring hospitalization, revascularization and stroke Secondary: Risk of death due to CHD, nonfatal MI or re-vascularization; risk of the individual components of the primary endpoint; discontinuation rates; safety	favoring atorvastatin (95% CI, 5 to 26; P=0.005). Secondary: The risk of death due to CHD, nonfatal MI or revascularization was reduced by 14% with atorvastatin (P=0.029) with a two year event rate of 19.7% compared to a two year event rate of 22.3% with pravastatin. The risk of death, MI or urgent revascularization was reduced by 25% with atorvastatin (P<0.001). Among the individual components of the primary endpoint, atorvastatin was associated with a significant reduction of 14% for revascularization (P=0.04) and a 29% reduction in the risk of recurrent unstable angina (P=0.02) compared to pravastatin. There were nonsignificant reductions in the rates of death or MI (18%, P=0.06) and the rates of stroke (P value not reported) between the two treatments. The discontinuation rates due to adverse events or for other reasons were 21.4 and 22.8% with pravastatin and atorvastatin at one year (P=0.30) and 33.0 and 30.4%, respectively at two years (P=0.11). Discontinuation rates due to myalgias or muscle aches or elevations in CK levels were 2.7 and 3.3% with pravastatin and atorvastatin (P=0.23). There were 1.1 and 3.3% of patients receiving pravastatin and atorvastatin who had elevations in ALT levels that were at least three times the upper limit of normal (P<0.001).
Ray et al.[226] (2005) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day	Subanalysis of PROVE IT-TIMI 22 Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240	N=4,162 Up to 3 years (mean, 2 years)	Primary: A composite of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization or stroke Secondary: A composite of death, MI or unstable angina	Primary: After 30 days, 3.0 and 4.2% of patients receiving atorvastatin and pravastatin experienced a primary endpoint (HR, 72; 95% CI, 0.52 to 0.99; P=0.046). From six months to the end of the trial, 15.1 and 17.7% of patients receiving atorvastatin and pravastatin experienced a primary endpoint (HR, 82; 95% CI, 0.69 to 0.99; P=0.037). Secondary: Atorvastatin was associated with a significant reduction in the risk of the triple composite endpoint compared to pravastatin (15.7 vs 20.0%; HR, 76; 95% CI, 0.66 to 0.88; P=0.0002). After 30 days, patients receiving atorvastatin experienced a significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(standard regimen)	mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL		requiring hospitalization	greater reduction in LDL-C and hsCRP level compared to patients receiving pravastatin (P<0.001 for both).
Ahmed et al.[227] (2006) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22 Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24	N=4,162 Up to 3 years (mean, 2 years)	Primary: A composite of death, MI, unstable angina requiring hospitalization, revascularization with PCI or CABG surgery occurring within 30 days after randomization or stroke within two years after trial onset Secondary: A composite of death, MI or unstable angina requiring	Primary: There was no significant difference between the two treatments in terms of the primary endpoint among patients with diabetes (31.8 vs 28.4%; HR, 88; P=0.28). Secondary: Atorvastatin was associated with a significantly lower rate for the secondary composite endpoint compared to pravastatin among patients with diabetes (21.1 vs 26.6%; HR, 0.75; P=0.03) and patients without diabetes (14 vs 18%; HR, 0.76; P=0.002). Consequently, treating 1,000 diabetic and nondiabetic patients with atorvastatin would prevent 55 and 40 events, respectively (P value not reported). Compared to nondiabetic patients, fewer patients with diabetes receiving atorvastatin achieved the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L (37.6 vs 45.4%; P=0.004). Out of diabetic patients receiving atorvastatin, 62% failed to reach the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL, stratified by type 2 diabetes		hospitalization; LDL-C <70 mg/dL goal; hsCRP <2 mg/L goal; MI; unstable angina requiring hospitalization	Diabetic patients who reached the dual LDL-C and CRP goals had significantly lower rates of the secondary endpoint compared to patients who failed to reach the goal (17.7 vs 24.7%; P=0.021). In the diabetic population, among the individual components of the primary and secondary composite endpoints, the only variable exhibiting a significant reduction with atorvastatin compared to pravastatin was unstable angina requiring hospitalization (3.1 vs 7.4%; P=0.003).
Scirica et al.[228] (2006) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22 Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC	N=4,162 Up to 3 years (mean, 2 years)	Primary: Hospitalization for heart failure occurring ≥30 days after randomization Secondary: Not reported	Primary: Atorvastatin was associated with a significant reduction in the rate of hospitalization for heart failure compared to pravastatin (1.6 vs 3.1%; HR, 0.55; 95% CI, 0.35 to 0.85; P=0.008). The benefit observed with atorvastatin was independent on recurrent MI or prior history of heart failure. Higher BNP was associated with an increased risk for heart failure (HR, 2.6; 95% CI, 1.2 to 5.5; P=0.016). Among patients with a high BNP level (>80 pg/mL), atorvastatin was associated with a lower incidence of heart failure compared to pravastatin (HR, 0.32; 95% CI, 0.13 to 0.8; P=0.014). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	≤200 mg/dL			
Ray et al.[229] (2006) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22 Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL, stratified by age (<75 years of age and ≥75 years of age)	N=4,162 Up to 3 years (mean, 2 years)	Primary: Cardiac mortality; MI; unstable angina requiring hospitalization; relationship between NCEP goal and a composite primary endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, re-vascularization or stroke Secondary: A composite of death, MI or unstable angina requiring hospitalization	Primary: At 30 days, a greater proportion of patients in both age groups receiving atorvastatin achieved the NCEP goals compared to patients in both age groups receiving pravastatin (P<0.001). Among patients ≥75 years of age, the achievement of the NCEP LDL-C goal was associated with an eight percent reduction in the risk of primary endpoint from baseline (P=0.008). The younger age group achieving the NCEP LDL-C goal was associated with a 2.3% reduction in the risk of primary endpoint from baseline (P=0.013). Patients <75 years of age were associated with a lower risk of the primary composite endpoint compared to patients ≥75 years of age (23.0 vs 30.4%; P<0.0001). Patients <75 years of age were associated with a lower risk of all-cause mortality (P<0.0001), MIs (P<0.0001), unstable angina requiring hospitalization (P=0.01) or strokes (P=0.004) compared to patients ≥75 years of age. Secondary: The composite triple endpoint occurred more frequently in patients ≥75 years of age (20.1 vs 11.0%; HR, 1.93; 95% CI, 1.59 to 2.33; P<0.0001).
Deedwania et al.[230] (2007)	DB, DD, MC, PG, RCT	N=893 12 months	Primary: Absolute change from	Primary: After 12 months, the total duration of ischemia was significantly reduced from baseline with both treatments (P<0.001). There was no significant difference

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
SAGE Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Ambulatory patients 65 to 85 years of age with CAD, ≥1 episode of myocardial ischemia that lasted ≥3 minutes during a 48 hour ambulatory ECG at screening and baseline LDL-C 100 to 250 mg/dL		baseline in the total duration of myocardial ischemia on 48 hour Holter monitor Secondary: Absolute change from baseline to month three in the total duration of myocardial ischemia on 48 hour Holter monitor; percent change from baseline to months three and 12 in the total duration of myocardial ischemia; absolute and percent changes from baseline to months three and 12 in the number of ischemic episodes; percent change in ischemic burden; proportion of	between the two treatments in terms of the primary endpoint (P=0.88). Secondary: There were no significant differences between the two treatments in any of the secondary endpoints assessing degree of ischemia at months three and 12 (P value not reported). Atorvastatin was associated with a significant 77% reduction in all-cause mortality compared to pravastatin (HR, 0.33; 95% CI, 0.13 to 0.83; P=0.014). Compared to pravastatin, atorvastatin was associated with significantly greater reductions in TC, LDL-C, TG and apo B at months three and 12 (P<0.001). Compared to atorvastatin, pravastatin was associated with a significantly greater increase in HDL-C at three (P<0.001) and 12 months (P=0.009). Atorvastatin was associated with a significantly higher incidence of liver test abnormalities (17.3 vs 13.9%; P<0.001). There were no significant differences between pravastatin and atorvastatin in treatment related adverse events (13.9 vs 17.3%; P=0.17).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			patients free of ischemia at months three and 12; percent changes in the levels of TC, LDL-C, HDL-C, TG and apo B	
Pitt et al.[231] (2012) LUNAR Atorvastatin 80 mg/day vs rosuvastatin 20 mg/day vs rosuvastatin 40 mg/day	MC, OL, PG, PRO, RCT Patients 18 to 75 years of age with CAD who were hospitalized for ACS within 48 hours of ischemic symptoms with non-ST-segment elevation ACS or ST-segment elevation ACS who received optimal reperfusion therapy (successful treatment with a thrombolytic agent or primary catheter-based intervention initiated within 12 hours of symptom onset), LDL cholesterol level >70 mg/dL and a fasting TG level	N=825 12 weeks	Primary: Averaged LDL reduction measurements at six and 12 weeks Secondary: Percentage reduction from baseline in LDL at two, six and 12 weeks, percentage change in TC, HDL, apo AI, apo B, LDL:HDL cholesterol, TC/HDL, non-HDL:HDL-C, apo B:apo AI, change in CRP at six and 12 weeks and safety	Primary: The averaged week six and 12 LDL reduction from baseline was significantly greater with rosuvastatin 40 mg compared to atorvastatin 80 mg (46.8 vs 42.7%; P<0.05). The reduction from baseline with rosuvastatin 20 mg was -42.0%. Secondary: Compared to treatment with atorvastatin 80 mg, LDL was significantly reduced with rosuvastatin 20 mg at two weeks (P<0.01) and weeks six through 12 (P<0.05 for both). Similarly, rosuvastatin 40 mg significantly lowered LDL compared to atorvastatin 80 mg at weeks two, six and 12 (P<0.01 for all). The percent change in TC was significantly greater with rosuvastatin 20 mg compared to atorvastatin 80 mg (-28.6 vs 30.9%; P<0.05). Rosuvastatin 40 mg reduced TC from baseline by 32.2%. Both the 20 and 40 mg dose of rosuvastatin significantly increased HDL compared to atorvastatin 80 mg (9.7 and 11.9 vs 5.6%; P<0.01 for both rosuvastatin doses). Apo AI was significantly higher following treatment with rosuvastatin 20 and 40 mg compared to atorvastatin 80 mg (10.3 and 10.1 vs 4.2, respectively; P<0.01 for both rosuvastatin doses). There were no statistically significant differences between either dose of rosuvastatin and atorvastatin 80 mg with regard to decrease in Apo B over 12 weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	<500 mg/dL within 72 hours of symptom onset			The ratio of LDL:HDL decreased in all three groups, however, rosuvastatin 40 mg was associated with a greater percentage reduction compared to atorvastatin 80 mg (-51.5 vs 44.5%; P<0.001). Rosuvastatin 40 mg significantly reduced the ratio of TC:HDL compared to atorvastatin 80 mg (-38.2 vs 33.1%; P<0.001). Rosuvastatin 20 mg reduced the TC/HDL ratio by 34.0%. Rosuvastatin 40 mg also significantly improved the ratio of non-HDL:HDL compared to atorvastatin 80 mg (-47.3 vs -41.2%; P<0.001). Rosuvastatin 20 mg reduced the non-HDL:HDL ratio by -42.3%. The ratio of apo B:apo AI was significantly reduced with rosuvastatin 40 mg compared to atorvastatin 80 mg (P<0.001). The percent change in CRP at week 12 was >80% in all groups; however, there was no statistically significant difference between the treatments.
Pedersen et al.[232] (2005) IDEAL Atorvastatin 80 mg/day vs simvastatin 20 to 40 mg/day	MC, OL, PG, RCT Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines	N=8,888 4.8 years	Primary: Incidence of a major coronary event (CHD death, nonfatal MI or cardiac arrest with resuscitation) Secondary: Major cardiovascular events (any primary event plus stroke), any CHD event (any primary event, any coronary revascularizatio	Primary: Atorvastatin was associated with a nonsignificant reduction in the risk of a major coronary event compared to simvastatin (9.3 vs 10.4%; HR, 0.89; P=0.07). Secondary: Atorvastatin was associated with a significant reduction in the risk of a nonfatal MI compared to simvastatin (6.0 vs 7.2%; HR, 0.83; P=0.02). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; P=0.02). Atorvastatin was associated with a significant reduction in the risk of any CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; P<0.001). Atorvastatin was associated with a significant reduction in the risk of any cardiovascular events compared to simvastatin (26.5 vs 30.8%; HR, 0.84; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			n procedure or hospitalization for unstable angina), any cardiovascular events (any of the former plus hospitalization with a primary diagnosis of CHF and PAD), all individual endpoints, all-cause mortality	Atorvastatin was associated with a significant reduction in the risk of peripheral vascular disease compared to simvastatin (2.9 vs 3.8%; HR, 0.76; P=0.02). Atorvastatin was associated with a nonsignificant reduction in the risk of fatal or nonfatal stroke compared to simvastatin (3.4 vs 3.9%; HR, 0.87; P=0.20). Atorvastatin was associated with a nonsignificant reduction in the risk of hospitalization for nonfatal heart failure compared to simvastatin (2.2 vs 2.8%; HR, 0.81; P=0.11). Atorvastatin was associated with a nonsignificant reduction in the risk of death from cardiovascular or noncardiovascular cause compared to simvastatin (4.9 vs 5.0; HR, 1.03; 95% CI, 0.85 to 1.24; P=0.78 and 3.2 vs 3.5%; HR, 0.92; P=0.47). Atorvastatin was associated with a nonsignificant reduction in the risk of all-cause mortality compared to simvastatin (8.2 vs 8.4%; HR, 0.98; P=0.81). Atorvastatin was associated with a higher rate of drug discontinuations due to adverse effects compared to simvastatin (9.6 vs 4.2%; P<0.001). Atorvastatin was associated with a higher rate of liver transaminase elevations compared to simvastatin (P<0.001). There was no significant difference between the two treatments in the incidence of serious adverse events (P=0.42).
Tikkanen et al.[233] (2009) IDEAL Atorvastatin 80 mg/day vs	Post hoc analysis of IDEAL Adult patients with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines;	N=8,888 4.8 years	Primary: Incidence of a major coronary event (coronary death, confirmed nonfatal acute MI or cardiac arrest with	Primary: There was no significant heterogeneity of treatment effect by age for any composite endpoint, indicating that the benefit of atorvastatin was similar for younger and older patients. Nevertheless, the cardiovascular risk reductions associated with atorvastatin tended to be numerically lower in the older than younger age group. Atorvastatin was associated with a 20% decrease in risk of the primary endpoint of major coronary events in patients <65 years of age (HR, 0.80; 95% CI, 0.66 to 0.98), with similarly significant reductions in secondary composite endpoints.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 20 to 40 mg/day	stratified by age (<65 years of age vs ≥65 years of age)		resuscitation) Secondary: Major cardiovascular events (any primary event and stroke), any CHD event (any primary event, any coronary re-vascularization procedure, any hospitalization for unstable angina), any cardiovascular events	Secondary: There were similarly significant reductions in secondary composite endpoints, the corresponding reductions in the risk in patients ≥65 years of age were four to 12%, and significance was achieved for only the endpoint of any cardiovascular event in older patients (HR, 0.88; 95% CI, 0.79 to 0.99).
Strandberg et al.[234] (2009) IDEAL Atorvastatin 80 mg/day vs simvastatin 20 mg/day	Post hoc analysis of IDEAL Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines	N=8,888 4.8 years	Primary: Hospitalization for heart failure Secondary: Not reported	At baseline, a history of heart failure (NYHA class I to IIIa) was reported by 537 patients, 5.5 (n=244) and 6.6% (n=293) of patients receiving simvastatin and atorvastatin, respectively. Primary: During the trial, there were 222 new hospitalizations for heart failure. Incidences of hospitalization for heart failure were 10.6 (57/537) vs 2.0% (165/8,351) in patients with and without a history of heart failure. Of the new cases, most were not preceded by an in-trial MI. Of the 222 patients with new hospitalization for heart failure during the trial, 71 (32.0%) patients subsequently died. Among the 222 new hospitalizations, 123 (2.8%) occurred with simvastatin compared to 99 (2.2%) with atorvastatin (HR, 0.81; 95% CI, 0.62 to 1.05; P=0.11). Of the 537 patients with heart failure at baseline, 104 died during the trial compared to 36 of the patients without a history of heart failure (HR, 2.66; 95% CI, 2.16 to 3.27; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				After adjustments in the entire trial cohort, atorvastatin was associated with a 26% decrease (P=0.03) of new or recurrent heart failure events compared to simvastatin. Atorvastatin tended to be associated with fewer recurrent heart failure events in those with heart failure at baseline (n= 537; P=0.11) and in those without heart failure at baseline (n=8,351; P=0.15). Secondary: Not reported
Stoekenbroek et al.[235] (2015) IDEAL Atorvastatin 80 mg/day vs simvastatin 20 to 40 mg/day	MC, OL, PG, RCT Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines	N=8,888 4.8 years	Primary: PAD incidence Secondary: Posthoc analysis of the impact of baseline PAD on clinical outcomes: the rate of major coronary events (defined as coronary death, hospitalization for non-fatal MI or cardiac arrest with resuscitation) with high-dose versus usual-dose statins	Primary: During the study, incident PAD occurred in 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin (HR, 0.70; 95% CI, 0.53 to 0.91; P=0.007). Secondary: For patients with PAD at baseline, the rate of major coronary events during the study was non-significantly lower in the atorvastatin group (14.4%) compared with the simvastatin group (20.1%) (HR, 0.68; 95% CI, 0.41 to 1.11; P=0.13). A significant treatment effect for atorvastatin was seen for reduction of overall cardiovascular (P=0.046) and coronary events (P=0.004) and coronary revascularization (P=0.007) in these patients. Among participants without a history of PAD, treatment with atorvastatin resulted in a non-significant reduction in major coronary events (HR, 0.91; 95% CI, 0.79 to 1.04; P=0.16), and significantly reduced the risk of major cardiovascular events (HR, 0.88; 95% CI, 0.78 to 1.00; P=0.046), any coronary event (HR, 0.86; 95% CI, 0.78 to 0.94; P=0.001), any cardiovascular event (HR, 0.85; 95% CI, 0.78 to 0.92; P<0.001), non-fatal MI (HR, 0.84; 95% CI, 0.71 to 1.00; P=0.046), coronary revascularization (HR, 0.79; 95% CI, 0.70 to 0.88; P<0.001) and PAD (HR, 0.70; 95% CI, 0.53 to 0.91; P=0.007), compared with simvastatin treatment. Atorvastatin significantly reduced the incidence of any coronary heart event and coronary revascularization in both patients with and without PAD at baseline. Compared with patients without PAD at baseline, the incremental benefit of atorvastatin appeared to be larger for patients with previous PAD. However, the only outcomes for which the interaction terms reached the prespecified level of significance were any coronary heart event and coronary

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				revascularization (P for interaction, 0.042 and 0.090, respectively). The incremental LDL-C reduction observed among patients treated with atorvastatin compared with simvastatin did not significantly differ between patients with or without PAD at baseline (P for interaction, 0.209).
Sakamoto et al.[236] (2007) MUSASHI-AMI Lipophilic statins (mean daily doses; atorvastatin 9.3 mg, fluvastatin 26.8 mg, pitavastatin 2 mg, simvastatin 5 mg) vs hydrophilic statin (mean daily dose; pravastatin 9.4 mg) All medications were administered within 96 hours of hospital admission with an acute MI.	MC, RCT Adult patients randomized to statin or no statin therapy within 96 hours of an acute MI, with TC 190 to 240 mg/dL	N=486 416 days	Primary: Composite of ACS events (cardiovascular death, nonfatal MI, recurrent acute myocardial ischemia requiring emergency hospitalization) Secondary: Incidence of individual components of the primary endpoint, nonfatal stroke, heart failure requiring emergent rehospitalization, new Q-wave appearance on the ECG	Primary: Hydrophilic statin therapy was associated with a nonsignificant lower incidence of ACS events compared to lipophilic statin therapy (3.6 vs 9.9%; P=0.053). Secondary: Hydrophilic statin therapy was associated with a significantly lower incidence of new Q-wave appearance on the ECG compared to lipophilic statin therapy (75% vs 89%; P=0.0056). There was no difference between the two treatments in any of the other secondary endpoints (P=0.339).
Choi et al.[237] (2014)	OBS, RETRO Patients with first-	N=535 Mean follow-up	Primary: Time to mortality and	Primary: Among the 535 patients, 295 (55.1%) were not prescribed a statin, 125 (23.4%) were prescribed a low-potency statin, and 115 (21.5%) were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Nonstatin vs low-potency statin vs high-potency statin	ever cardioembolic stroke	of 22.2 months	time to recurrent stroke Secondary: Not reported	prescribed a high-potency statin. Forty-two patients died (35 from the nonstatin group, 5 from the low-potency group, and 2 from the high-potency group): 11 from cardiac disease, 11 from recurrent stroke, 13 from other causes (including infection and cancer), and 7 from unknown causes. With regard to recurrent stroke, 40 patients had a recurrence (29 from the nonstatin group, 12 from the low-potency group, and 7 from the high-potency group). In patients with cardioembolic stroke, statin therapy was independently associated with reduced mortality. Kaplan–Meier estimation shows that either low- or high-potency statin therapy was associated with reduced mortality (log-rank test; P=0.006). Secondary: Not reported
Afilalo et al.[238] (2007) Moderate statin therapy (pravastatin ≤40 mg/day, lovastatin ≤40 mg/day, fluvastatin ≤40 mg/day, simvastatin ≤20 mg/day, atorvastatin ≤10 mg/day, rosuvastatin ≤5 mg/day) vs intensive statin therapy (simvastatin 80	MA (6 RCTs) Patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=28,505 ≥6 months	Primary: All-cause mortality, CHD mortality, hospitalization for heart failure, major coronary event (cardiovascular death or ACS), stroke, adverse effects Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with lower all-cause mortality (OR, 0.75; 95% CI, 0.61 to 0.93). By treating 90 people with intensive statin therapy, one death could be prevented. All-cause mortality was not reduced by intensive statin therapy among patients with stable CHD (OR, 0.99; 95% CI, 0.89 to 1.11). In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.86; 95% CI, 0.73 to 1.01). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.82; 95% CI, 0.75 to 0.91). Treating 46 patients with intensive statin therapy may prevent one major coronary event. In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.63; 95% CI, 0.46 to 0.86).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day, atorvastatin 80 mg/day, rosuvastatin 20 to 40 mg/day)				In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.77; 95% CI, 0.64 to 0.92). Treating 112 patients with intensive statin therapy may prevent one hospitalization for heart failure. Intensive statin therapy was associated with a threefold increase in adverse hepatic (OR, 3.73; 95% CI, 2.11 to 6.58) and muscular events (OR, 1.96; 95% CI, 0.50 to 7.63). Consequently, 96 people would need to be treated, for one patient to experience an adverse hepatic event. Secondary: Not reported
Cannon et al.[239] (2006) Intensive statin therapy (simvastatin 40 to 80 mg/day, atorvastatin 80 mg/day) vs moderate statin therapy (pravastatin 40 mg/day, simvastatin 20 mg/day, atorvastatin 10 mg/day)	MA (4 RCTs) Patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=27,548 (4 studies) Up to 5 years	Primary: Combined incidence of coronary death or nonfatal MI; the combined incidence of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina or re-vascularization); incidence of stroke; incidence of cardiovascular, noncardiovascular and all-cause mortality	Primary: Intensive statin therapy was associated with a significant odds reduction of 16% for coronary death or MI compared to moderate statin therapy (9.4 vs 8.0%; OR, 0.84; 95% CI, 0.77 to 0.91; P<0.00001). Intensive statin therapy was associated with a significant odds reduction of 16% for coronary death or any cardiovascular event compared to moderate statin therapy (32.3 vs 28.8%; OR, 0.84; 95% CI, 0.80 to 0.89; P<0.0000001). Intensive statin therapy was associated with a nonsignificant reduction in cardiovascular mortality of 12% compared to moderate statin therapy (3.8 vs 3.3%; OR, 0.88; 95% CI, 0.78 to 0.1.00; P=0.054). Intensive statin therapy was associated with a nonsignificant lower rate of noncardiovascular mortality compared to moderate statin therapy (P=0.73). Intensive statin therapy was associated with a nonsignificant significant reduction in all-cause mortality compared to moderate statin therapy (6.2 vs 5.9%; P=0.20). Intensive statin therapy was associated with a significant overall odds reduction of 18% for stroke compared to moderate statin therapy (2.8 vs 2.3%; OR, 0.82; 95% CI, 0.71 to 0.96; P=0.012).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			Secondary: Not reported	Intensive statin therapy was associated with a significant odds reduction of 16.5% for CHD death or MI compared to moderate statin therapy (OR, 0.835; 95% CI, 0.77 to 0.91; P<0.0001). Secondary: Not reported
Murphy et al.[240] (2007) Intensive statin therapy (simvastatin 40 to 80 mg/day, atorvastatin 80 mg/day) vs moderate statin therapy (pravastatin 40 mg/day, simvastatin 20 mg/day)	MA (2 RCTs) Patients with recent ACS, clinically stable for 12 to 24 hours, randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=8,658 Up to 2 years	Primary: Incidence of cardiovascular, non-cardiovascular and all-cause mortality Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant 23% reduction in the risk of all-cause mortality compared to moderate statin therapy (3.6 vs 4.9%; HR, 0.77; 95% CI, 0.63 to 0.95; P=0.015). Intensive statin therapy was associated with a significant 24% reduction in the risk of cardiovascular mortality compared to moderate statin therapy (2.6 vs 3.5%; HR, 0.76; 95% CI, 0.59 to 0.97; P=0.025). Intensive statin therapy was associated with a nonsignificant reduction in the risk of noncardiovascular mortality compared to moderate statin therapy (1.0 vs 1.4%; HR, 0.82; 95% CI, 0.55 to 1.21; P=0.32). Secondary: Not reported
Combination Products				
Hypercholesterolemia (Combination Products)				
Erdine et al.[241] (2009) Gemini-AALA Amlodipine-atorvastatin 5- or 10-10, 20, 40 or 80 mg/day	OL, PRO Patients 18 to 80 years of age with concurrent HTN and dyslipidemia	N=1,649 14 weeks	Primary: Proportion of patients achieving both BP and LDL-C goals Secondary: Absolute and	Primary: More than half (55.2%) of patients achieved both their BP and LDL-C goals at the end of 14 weeks. A higher proportion of patients in Groups 1 and 2 achieved both goals compared to patients in Group 3 (81.3 and 78.8 vs 40.3%). When patients in Group 3 without diabetes (n=407) were further analyzed using a BP goal <140/90 mm Hg, goal achievement for both BP and LDL-C in nondiabetic patients rose to 70.0%. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
All possible dosing combinations were evaluated. Patients were classified into 1 of 3 cardiovascular risk categories. Group 1: HTN and dyslipidemia with no additional cardiovascular risk factors (BP goal: <140/90 mm Hg, LDL-C goal: <4.1 mmol/L). Group 2: HTN and dyslipidemia with ≥1 additional cardiovascular risk factor, excluding CHD and diabetes (BP goal: <140/90 mm Hg, LDL-C goal: <3.4 mmol/L). Group 3: HTN and dyslipidemia			percentage change from baseline in BP and lipid levels, BP and LDL-C goal attainment stratified by prior anti-hypertensive and lipid lowering medications	All doses achieved significant improvements in LDL-C, TG, HDL-C, TC, SBP and DBP (P<0.001 for all). The proportions of patients with no prior treatment for HTN and dyslipidemia in the cardiovascular risk categories were 74.1 (95% CI, 53.7 to 88.9), 81.6 (95% CI, 72.7 to 88.5) and 39.8% (95% CI, 30.0 to 50.2) for Groups 1, 2 and 3. The corresponding proportions for patients with prior treatment for HTN and dyslipidemia were 82.0 (95% CI, 68.6 to 91.4), 80.7 (95% CI, 73.1 to 87.0) and 39.5% (95% CI, 35.3 to 43.8). The corresponding proportions for patients with no prior treatment for dyslipidemia were 80.2 (95% CI, 69.9 to 88.3), 77.8 (95% CI, 73.0 to 82.2) and 40.9% (95% CI, 36.1 to 45.7). The corresponding proportions for patients with prior treatment for dyslipidemia were 82.8 (95% CI, 70.6 to 91.4), 80.9 (95% CI, 73.8 to 86.8) and 39.8% (95% CI, 35.9 to 43.9). The corresponding proportions for patients with no prior treatment for HTN were 77.1 (95% CI, 59.9 to 89.6), 81.7 (95% CI, 73.6 to 88.1) and 41.1% (95% CI, 33.1 to 49.3). The corresponding proportions for patients with prior treatment for HTN were 82.7 (95% CI, 74.0 to 89.4), 77.9 (95% CI, 73.3 to 82.0) and 40.1% (95% CI, 36.8 to 43.5). The corresponding proportions for patients with prior treatment for HTN only were 83.3 (95% CI, 70.7 to 92.1), 76.2 (95% CI, 70.2 to 81.5) and 41.2% (95% CI, 35.8 to 46.8). The corresponding proportions of patients with prior treatment for dyslipidemia only were 87.5 (95% CI, 47.3 to 99.7), 82.4 (95% CI, 56.6 to 96.2) and 43.4% (95% CI, 29.8 to 57.7).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
with CHD or CHD risk equivalent (diabetes or other atherosclerotic disease (BP goal: <130/80 mm Hg, LDL-C goal: <2.6 mmol/L).				
Flack et al.[242] (2008) CAPABLE Amlodipine-atorvastatin 5- or 10-10, 20, 40, or 80 mg/day All possible dosing combinations were evaluated.	MC, OL African American patients 18 to 80 years of age with uncontrolled HTN and dyslipidemia	N=489 20 weeks	Primary: Proportion of patients in three cardiovascular risk groups (Group 1: patients without additional risk factors; Group 2: patients with >1 additional risk factors, excluding CHD and diabetes and Group 3: patients with CHD or CHD risk equivalent) who achieved the JNC 7 and NCEP ATP III goals Secondary: Changes from baseline in SBP, DBP,	Primary: More patients in Groups 1 and 2 achieved both goals compared to patients in Group 3 (69.7, 66.7 and 28.2%, respectively; P value not reported). Secondary: Combination therapy was associated with a 17.5 and 10.1 mm Hg decrease in the SBP and DBP, respectively (P value not reported). Combination therapy was associated with a 23.6% reduction in LDL-C (P value not reported). Combination therapy was associated with a 17% reduction in TC (P value not reported). Combination therapy was associated with a 2.2% increase in HDL-C (P value not reported). Combination therapy was associated with a 6.9% reduction in TG (P value not reported). Combination therapy was associated with a 19.3% reduction in apo B (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			LDL-C, TC, TG, HDL-C and apo B	
Hobbs et al.[243] (abstract) (2009) Amlodipine-atorvastatin 5- or 10-10, 20, 40 or 80 mg/day All possible dosing combinations were evaluated.	2 MC, OL Patients with uncontrolled BP and controlled/uncontrolled LDL-C qualifying for treatment according to local governing guidelines	N=2,245 16 weeks	Primary: Proportion of patients achieving country-specific BP and LDL-C goals, safety Secondary: Not reported	Primary: Within the two trials, 62.9 and 50.6% of patients achieved both country-specific BP and LDL-C goals. BP was reduced by 20.4/10.7 and 21.8/12.6 mm Hg in the two trials, respectively, and reductions in LDL-C were 34.8 and 42.2 mg/dL, respectively. The most common adverse events were peripheral edema (11.0%), joint swelling (2.9%) and headache (2.9%), of which, only edema was linked to trial medication. Secondary: Not reported
Neutel et al.[244] (2009) CUSP Amlodipine-atorvastatin 5-20 mg/day vs placebo All patients also received lifestyle changes. After 4 weeks, add-on antihypertensive and/or lipid lowering therapy	DB, MC, PC, RCT Patients ≥21 years of age with coexisting HTN (140 to 168/90 to 105 mm Hg) and dyslipidemia (LDL-C 110 to 160 mg/dL), without a history of cardiovascular disease who have never received treatment in the 3 months prior to enrollment	N=130 8 weeks	Primary: Proportion of patients who achieved both BP (<140/90 mm Hg) and LDL-C (<100 mg/dL) goals at week four Secondary: Proportion of patients who achieved both BP and LDL-C goals at week eight; proportion of patients who achieved both BP and LDL-C	Primary: After four weeks, the proportion of patients who achieved both BP and LDL-C goals was significantly greater with combination therapy compared to placebo (47.6 vs 1.7%; OR, 59.8; 95% CI, 7.4 to 486.0; P<0.001). Secondary: After eight weeks, the proportion of patients who achieved both BP and LDL-C goals was significantly greater with combination therapy compared to placebo (55.6 vs 5.0%; OR, 23.8; 95% CI, 6.7 to 85.0; P<0.001). After four and eight weeks, the proportion of patients who achieved the BP goal was significantly greater with combination therapy compared to placebo (P=0.001 and P=0.006). After four and eight weeks, the proportion of patients who achieved the LDL-C goal was significantly greater with combination therapy compared to placebo (P<0.001 for both). Mean reductions in SBP (13.3 vs 5.6 mm Hg) and DBP (9.4 vs 4.2 mm Hg) at week four was significantly greater with combination therapy (P<0.001). The mean percentage change in LDL-C (35.6 vs +3.3%) at week four was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
was permitted.			goals at both weeks four and eight; proportion of patients who achieved the LDL-C goal at weeks four and eight; mean changes from baseline in SBP, DBP and LDL-C at weeks four and eight; 10 year Framingham risk of CHD at weeks four and eight	significantly greater with combination therapy (P<0.001). These benefits were maintained throughout eight weeks of treatment. With placebo, 10 year Framingham risk of CHD increased by 4.1% both at weeks four and eight relative to baseline. With combination therapy, the risk of future cardiac events over the next 10 years decreased by 33 and 38% at weeks four and eight, respectively, relative to baseline (P<0.001 vs placebo).
Grimm et al.[245] (2010) TOGETHER Amlodipine-atorvastatin 5- to 10-20 mg/day vs amlodipine 5 to 10 mg/day All patients received therapeutic lifestyle changes.	DB, DD, PRO, RCT Patients ≥21 years of age with HTN, no history of cardiovascular disease or diabetes and ≥2 of the following risk factors: age ≥45 years if male and ≥55 years if female; current smoker; a family history of premature CHD in a first-degree	N=245 6 weeks	Primary: Proportion of patients achieving both BP (<140/90 mm Hg) and LDL-C (<100 mg/dL) goals Secondary: Proportion of patients achieving both BP and LDL-C goals at four weeks; proportion of patients	Primary: The proportion of patients achieving both BP and LDL-C goals at six weeks was 67.8 vs 9.6% with combination therapy and amlodipine (risk difference, 58.2; 95% CI, 48.1 to 68.4; P<0.001; OR, 19.0; 95% CI, 9.1 to 39.6; P<0.001). Secondary: The proportion of patients achieving both BP and LDL-C goals at four weeks was 62.9 vs 5.2% (risk difference, 57.7; 95% CI, 47.9 to 67.5; P<0.001; OR, 31.4; 95% CI, 12.6 to 78.1; P<0.001). LDL-C goal was achieved by 82.8 and 7.0% (risk difference, 75.8; 95% CI, 67.4 to 84.2; P<0.001; OR, 65.5; 95% CI, 27.1 to 158.3; P<0.001) at four weeks and 83.9 and 11.3% (risk difference, 72.6; 95% CI, 63.7 to 81.5; P<0.001; OR, 42.0; 95% CI, 19.4 to 91.0; P<0.001) at six weeks. The difference in the proportions of patients achieving the BP goal at weeks four and six were not significantly different between the two treatments (four weeks; OR, 1.1; P=0.785 and six weeks; OR, 1.5; P=0.171).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	relative; HDL-C <40 mg/dL; waist circumference 102 cm if male or 88 cm if female; all patients had been previously treated with amlodipine 5 or 10 mg with either controlled or Stage 1 HTN, fasting LDL-C ≥100 to ≤170 mg/dL		achieving the BP or LDL-C goal at weeks four and six; change from baseline in SBP, DBP, LDL-C, TC, TG and HDL-C at four and six weeks; predicted 10 year Framingham risk of CHD outcomes at four and six weeks; safety	There were significant mean percentage reductions from baseline in LDL-C, TC and TG with combination therapy compared to amlodipine at four and six weeks (P<0.001 for all comparisons). There was no difference in DBP between the two treatments and no difference in SBP at week four; however, at week six improvements in SBP were significantly greater with combination therapy compared to amlodipine (P=0.02). In patients receiving combination therapy, the 10 year Framingham risk for CHD at baseline was 8.2% and was reduced to 5.5 and 5.4% at weeks four and six compared to amlodipine (remained unchanged, 8.1%) (P<0.001). After four weeks, the percentage relative reduction from baseline in the 10 year Framingham risk for CHD in patients receiving combination therapy was 39.6% compared to 0.6% with amlodipine. After six weeks, the corresponding numbers were 42.0 and 4.5% (P<0.001). There were no deaths or serious adverse events reported during the trial. Overall, treatment-related adverse events occurred in 9.0 and 14.8% in patients receiving combination therapy and amlodipine, respectively. The majority of events with both treatments were mild. Changes in liver function test and creatinine phosphokinase were mild to moderate.
Bays et al.[246] Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10	DB, MC, RCT Patients 18 to 80 years of age with primary hypercholesterolemia with LDL-C >145 but ≤150 mg/dL and TG ≤350 mg/dL	N=1,528 24 weeks	Primary: Percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP;	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (53 vs 39%; P<0.001) and ezetimibe (53 vs 18.9%; P<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (P<0.001). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130, <100 or <70 mg/dL at 12 weeks compared to simvastatin (92.2, 78.6 and 38.7 vs 79.2, 45.9 and 7.0%, respectively; P<0.001 for al).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day vs placebo			proportion of patients reaching their NCEP ATP III LDL-C goal of <130, <100 or <70 mg/dL at 12 weeks	Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (P=0.607). Treatment-related adverse effects were similar in the pooled simvastatin, combination and ezetimibe groups, but were more frequent than placebo (14.8, 15.1, 12.8 and 8.1%, respectively; P values not reported).
Ose et al.[247] (2007) Simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients 22 to 83 years of age with primary hyper-cholesterolemia (LDL-C 145 to 250 mg/dL and TG <350 mg/dL)	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG, TC, non-HDL, hsCRP, LDL-C:HDL-C and TC:HDL-C; proportion of patients reaching LDL-C target (<100 or <70 mg/dL) Secondary: Not reported	Primary: Across all doses, combination therapy was associated with a significant reduction in LDL-C compared to simvastatin (53.7 vs 38.8%; P<0.001). Across all doses, combination therapy was associated with a significant reduction in TG, TC, non-HDL, hsCRP, LDL-C:HDL-C and TC:HDL-C compared to simvastatin (P<0.001 for all). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL compared to simvastatin (79.2 vs 47.9%; P<0.001). Similar results were observed with a LDL-C goal <70 mg/dL (30.4 vs 7.0%; P<0.001). The incidence of drug-related adverse effects was similar with combination therapy and simvastatin (7.4 vs 5.5%, respectively; P value not reported). Secondary: Not reported
Feldman et al.[248] (2006) Ezetimibe-	MA (3 DB, PC, RCTs) Patients with	N=3,083 28 weeks	Primary: Percent change from baseline in LDL-C, TG,	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C, TG, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). These affects did not differ

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	primary hypercholesterolemia		non-HDL-C, apo B and hsCRP; achievement of LDL-C <100 mg/dL at week-12 among patients <65 and ≥65 years of age Secondary: Not reported	between the older and younger patients (P value not reported). Combination therapy and simvastatin produced comparable increases in HDL-C (8 vs 7%, respectively; P value not reported). Significantly more patients, in all age groups, receiving combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 12 compared to patients receiving simvastatin (79 vs 42%; P<0.001). Similar results were observed with a LDL-C goal <70 mg/dL (37 vs 6%; P<0.001). Treatment-related adverse effects were similar with simvastatin and combination therapy, regardless of dose used and age group (P values not reported). Secondary: Not reported
Farnier et al.[249] (2007) Fenofibrate 160 mg/day vs ezetimibe-simvastatin10-20 mg/day plus fenofibrate 160 mg/day vs ezetimibe-simvastatin 10-20 mg/day	DB, MC, PA, PC, RCT Patients 18 to 79 years of age with mixed hyperlipidemia and no CHD or CHD risk equivalent disease, or a 10 year CHD risk >20% according to NCEP ATP III criteria	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Changes from baseline in TC, TG, non-HDL-C, HDL-C, apo AI and apo B	Primary: LDL-C was significantly reduced with triple therapy (-45.8%) compared to fenofibrate (-15.7%; P<0.01) or placebo (-3.5%; P<0.01), but not when compared to combination therapy (-47.1%; P>0.2). Secondary: HDL-C and apo AI were significantly increased with triple therapy (18.7 and 11.1%) compared to combination therapy (9.3 and 6.6%; P<0.01) or placebo (1.1 and 1.6%; P<0.01), but not when compared to fenofibrate (18.2 and 10.8%; P>0.2). TG, non-HDL-C and apo B were significantly reduced with triple therapy compared to all other active treatments (-50.0, -50.5 and -44.7%; P<0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo				
Farnier et al.[250] (2008) Fenofibrate 160 mg and ezetimibe-simvastatin 10-20 mg QD vs fenofibrate 160 mg QD vs ezetimibe-simvastatin 10-20 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 79 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or CHD risk score >20% (as defined by NCEP ATP III), LDL-C 130 to 220 mg/dL and TG 150 to 500 mg/dL	N=611 12 weeks	Primary: Percent change in cholesterol associated with lipoprotein subfractions (VLDL-C 1+2 and VLDL-C 3, IDL-C, LDL-C 1 to 4, Lp[a], HDL-C_2 and HDL-C_3, and changes in LDL particle size) Secondary: Not reported	Primary: The effects of ezetimibe-simvastatin, fenofibrate, and ezetimibe/simvastatin plus fenofibrate on VLDL subclasses were similar to those for VLDL-C overall. The maximal changes in IDL-C are achieved by ezetimibe-simvastatin with little additional effect of fenofibrate. Significant reductions were observed for all LDL-C subfractions with ezetimibe-simvastatin treatment. When coadministered with fenofibrate, the effects of both treatments were evident. Ezetimibe-simvastatin plus fenofibrate resulted in a pattern of changes that were similar to fenofibrate monotherapy indicating that the change in LDL-C pattern was primarily a function of fenofibrate. There was no significant difference in cholesterol associated with Lp(a) among the treatment groups. Fenofibrate and ezetimibe-simvastatin plus fenofibrate led to similar increases in median HDL-C_2 and HDL-C_3 compared to ezetimibe-simvastatin and placebo. Ezetimibe-simvastatin did not significantly affect LDL particle size. Fenofibrate and ezetimibe-simvastatin plus fenofibrate increased LDL particle size. At the end of the study, the percentages of patients exhibiting LDL size pattern B was 64, 49, 14, and 17% in the placebo, ezetimibe-simvastatin, fenofibrate, and ezetimibe-simvastatin plus fenofibrate groups, respectively. Secondary: Not reported
Robinson et al.[251] (2009)	DB, MC, PG, RCT Patients 18 to 79	N=1,128 6 weeks	Primary: Percentage of change from	Primary: After six weeks, the percent change in LDL-C was significantly greater with ezetimibe-simvastatin than with atorvastatin (all dose comparisons, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
VYMET Ezetimibe-simvastatin 10-20 to 10-40 mg QD vs atorvastatin 10 to 40 mg QD	years of age with metabolic syndrome and hypercholesterolemia who were at moderately high or high risk for coronary heart disease		baseline in LDL-C Secondary: Changes in other lipids, lipoprotein ratios, hsCRP, and attainment of prespecified lipid levels	Secondary: The percent of patients who achieved LDL-C <70 mg/dl and the non-HDL-C goal was significantly greater for ezetimibe-simvastatin than for atorvastatin (all dose comparisons, P<0.05). Treatment with ezetimibe-simvastatin led to a significantly greater reduction in TC, non-HDL-C, apo B, and all 4 lipid ratios compared to atorvastatin (all dose comparison, P<0.001). HDL-C cholesterol increased to a greater extent with ezetimibe/simvastatin 10/20 mg compared to atorvastatin 10 mg (P<0.05) and ezetimibe/simvastatin 10/40 mg compared to atorvastatin 40 mg (P<0.01). Changes in triglycerides, VLDL-C, apo AI, and hsCRP were comparable for both treatments, except that apo AI was significantly increased with ezetimibe-simvastatin 10-20 mg vs atorvastatin 10 mg (P<0.05). The rates of adverse events were similar for both treatments.
Ballantyne et al.[252] (2005) VYVA Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day	DB, MC, PG, RCT Patients ≥18 years of age with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with ≥2 risk factors conferring a 10 year risk >20% for CHD; with LDL-C ≥130 mg/dL, no CHD or its risk	N=1,902 6 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Percent change from baseline in LDL-C at each mg-equivalent statin dose comparison, percent change from baseline in HDL-C, proportion of patients	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (53.4 vs 45.3%; P<0.001). Secondary: Combination therapy (10/20 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 10 (50.6 vs 36.1%; P<0.001) and 20 mg (50.6 vs 43.7%; P<0.001). Combination therapy (10/40 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 40 mg (57.4 vs 48.3%; P<0.001). Combination therapy (10/80 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 80 mg (58.6 vs 52.9%; P<0.001). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to atorvastatin (7.9 vs 4.3%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	equivalent, and with ≥2 risk factors conferring a 10 year risk of <20% for CHD; with LDL-C ≥160 mg/dL and no CHD or its risk equivalent with <2 risk factors; with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT or AST <1.5 times the upper limit of normal, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the upper limit of normal and a HbA_{1c} <9.0% in patients with diabetes		achieving NCEP ATP III LDL-C goal (<100 mg/dL)	P<0.001). Averaged across all doses, a significantly greater proportion of patients receiving combination therapy achieved the NCEP ATP III LDL-C goal compared to atorvastatin (89.7 vs 81.1%; P<0.001). Averaged across all doses, a significantly greater proportion of patients with a CHD or a CHD risk equivalent receiving combination therapy achieved the NCEP ATP III LDL-C goals of <100 (85.4 vs 70.0%; P<0.001) and <70 mg/dL (45.3 vs 20.5%; P<0.001) compared to atorvastatin. Averaged across all doses, combination therapy was associated with a significant increase in the risk of ALT and AST elevation greater than three times the upper limit of normal compared to atorvastatin (P=0.006).
Ballantyne et al.[253] (2004) Ezetimibe-simvastatin 10-20 mg/day for weeks 1 to 6, titrated to 10-40 mg for weeks 7 to 18, titrated to 10-80 mg for	DB, MC, RCT Patients ≥18 years of age with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with	N=788 24 weeks	Primary: Mean percent change from baseline in LDL-C and HDL-C Secondary: Percent change from baseline to the ends of the second and	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (52.4 vs 45.1%; P<0.001). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to atorvastatin (12.3 vs 6.5%; P<0.001). Secondary: At the end of treatment period two, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (50.2 and 54.3 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
weeks 19 to 24 vs ezetimibe-simvastatin 10-10 mg/day for weeks 1 to 6, titrated to 10-20 mg/day for weeks 7 to 12, titrated to 10-40 mg/day for weeks 12 to 18, titrated to 10-80 mg/day for weeks 19 to 24 vs atorvastatin 10 mg/day for weeks 1 to 6, titrated to 20 mg/day for weeks 7 to 12, titrated to 40 mg/day for weeks 12 to 18, titrated to 80 mg/day for weeks 19 to 24	≥2 risk factors conferring a 10 year risk >20% for CHD; with LDL-C ≥130 mg/dL, no CHD or its risk equivalent, and with ≥2 risk factors conferring a 10 year risk of <20% for CHD; with LDL-C ≥160 mg/dL and no CHD or its risk equivalent with <2 risk factors; with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT or AST <1.5 times the upper limit of normal, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the upper limit of normal and a HbA_{1c} <9.0% in patients with diabetes		fourth six week treatment periods in LDL-C and HDL-C, safety	44.3%, respectively; P≤0.05). At the end of treatment period two, combination therapy (10/40 mg) was associated with a significant increase in HDL-C compared to atorvastatin (12.4 vs 6.9%; P≤0.05). At the end of treatment period four, combination therapy (10/40 mg) was associated with a significant reduction in LDL-C compared to atorvastatin (59.4 vs 52.5%, respectively; P≤0.05). At the end of treatment period four, combination therapy (10/40 mg) was associated with a significant increase in HDL-C compared to atorvastatin (12.3 vs 6.5%; P≤0.05). The safety of combination therapy was observed to be similar to that of atorvastatin (P value not reported).
Foody et al.[254] (2010) VYTELD Ezetimibe-	DB, MC, PG, RCT Patients ≥65 years of age with hyperlipidemia at	N=1,289 12 week	Primary: Percent change from baseline in LDL-C	Primary: Combination therapy achieved significantly greater percent decreases in LDL-C (-54.2 [10/20 mg] vs -39.5 [10 mg] and -46.6% [20 mg] and -59.1 [10/40 mg] vs -50.8% [40 mg]; P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 10-20 mg/day vs atorvastatin 10 or 20 mg/day AND Ezetimibe-simvastatin 10-40 mg/day vs atorvastatin 40 mg/day	moderately high risk or high risk (with CHD or CHD risk equivalents) with or without atherosclerotic vascular disease with LDL-C ≥130 mg/dL, TC ≤350 mg/dL, liver transaminases ≤1.5 times the upper limit of normal with no active liver disease and creatinine kinase ≤2 times upper limit of normal		Secondary: Proportion of patients achieving an LDL-C <70 and <100 mg/dL; percent change from baseline in TC, TG, HDL-C, non-HDL-C, VLDL-C, apo B, apo AI, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C and hsCRP; safety	Secondary: A significantly greater proportion of combination therapy-treated patients achieved an LDL-C goal <70 mg/dL (51.3 [10/20 mg] and 68.2% [10/40mg]; P<0.05) and <100 mg/dL (83.6 and 90.3%; P<0.001). Analysis based on risk demonstrated that a significantly greater proportion of high risk patients reached target LDL-C levels <70 mg/dL with combination therapy compared to atorvastatin (P<0.001 for all comparisons). Combined analysis of LDL-C level attainment based on atherosclerotic vascular disease status (<100 mg/dL for patients without atherosclerotic vascular disease and <70 mg/dL for patients with atherosclerotic vascular disease) demonstrated that a significantly greater proportion of patients reached the specified target with combination therapy compared to atorvastatin (P<0.001 for ezetimibe/simvastatin 10/20 mg vs atorvastatin 10 mg, P<0.05 for ezetimibe/simvastatin 10/20 vs atorvastatin 20 mg and ezetimibe/simvastatin 10/40 mg vs atorvastatin 40 mg). Improvements in non-HDL-C, TC, apo B and lipoprotein ratios were significantly greater with combination therapy (P<0.01 to P<0.001). Only ezetimibe/simvastatin 10/20 mg significantly improved HDL-C (P<0.001) levels compared to atorvastatin 20 mg and TG (P<0.01) and VLDL-C (P<0.05) levels compared to atorvastatin 10 mg. Improvements in apo AI and hsCRP levels did not differ among the various treatments (P values not reported). All doses of ezetimibe/simvastatin and atorvastatin were generally safe and well tolerated. The incidence of adverse events was similar between treatment groups. There were no serious drug-related adverse events observed during the trial.
Polis et al.[255] (2009) Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day	Post hoc analysis of 2 trials Patients with hypercholesterolemia not attaining NCEP ATP III LDL-C goals in	N=4,861 6 weeks	Primary: Percent change from baseline in LDL-C, proportion of patients achieving individual	Primary: Changes in LDL-C were generally similar regardless of diabetes/metabolic syndrome status or CHD risk strata in both trials. There was a significant effect by dose level in both trials in all condition and risk subgroups (P<0.001), with greater reductions observed with higher doses. NCEP ATP III LDL-C goal attainment was lowest in the high risk group with atherosclerotic vascular disease (12 to 64%) and greatest in the moderate and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 10, 20, 40 or 80 mg/day or rosuvastatin 10, 20 or 40 mg/day	patients with diabetes, metabolic syndrome or neither disease		LDL-C goals Secondary: Safety	low risk groups (84 to 100%). Secondary: All treatments were generally well tolerated, with overall similar safety regardless of disease and risk level.
Bardini et al.[256] (2010) LEAD Ezetimibe-simvastatin 10-20 mg/day vs simvastatin 40 mg/day	DB, DD, MC, PG, RCT Patients 18 to 75 years of age with type 2 diabetes for ≥12 months and documented CHD, or symptomatic peripheral vascular disease, who were taking a stable dose of simvastatin 20 mg/day for 6 weeks with good compliance and LDL-C ≥100 to ≤160 mg/dL	N=93 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Proportion of patients achieving LDL-C <100 mg/dL; percent change from baseline in TC, HDL-C and TG	Primary: Combination therapy produced a significantly greater reduction in LDL-C compared to simvastatin 40 mg (-32.2 vs -20.8%; P<0.01). Secondary: A nonsignificantly greater proportion of patients receiving combination therapy achieved an LDL-C <100 mg/dL (78.4 vs 60.0%; OR, 2.81; P=0.052). Combination therapy produced a significantly greater change compared to simvastatin 40 mg in TC (-20.6 vs -13.2%; P<0.01). Changes in HDL-C (0.85 vs 0.80%) and TG (-8.5 vs -1.8%) were similar between treatments (P values not reported).
Florentin et al.[257] (2011) Ezetimibe-simvastatin 10-10 mg/day vs simvastatin 40 mg/day	OL, RCT Patients with primary hypercholesterolemia with LDL-C levels above those recommended by the NCEP ATP III	N=100 3 months	Primary: Percent change from baseline in small density LDL-C Secondary: Percent change from baseline in lipid parameters, HOMA index	Primary: Both treatments decreased small density LDL-C (-42 vs -46%; P<0.000 vs baseline for both), with no significant difference between the two treatments (P value not reported). Secondary: Both treatments decreased TC (-31 vs -36%), LDL-C (-43 vs -49%), TG (-17 vs -19%), non-HDL-C (-40 vs -46%) and large LDL-C (-40 vs -44%) (P<0.000 vs baseline for all). Both treatments increased LDL particle size (0.5 vs 0.7%; P<0.05 vs baseline for both). Changes in TC, LDL-C and non-HDL-C were significantly greater with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			and hsCRP	combination therapy (P<0.05 for all), while changes in TG, large LDL-C, and LDL particle size were similar (P values not reported). No significant changes were observed in HOMA index with either treatment, and hsCRP decreased by 23% (P<0.05 vs baseline) with both treatments.
Rotella et al.[258] (2010) Ezetimibe-simvastatin 10-20 mg/day vs simvastatin 40 mg/day	2 DB, MC, RCT Patients ≥18 to ≤75 years of age with documented CHD or symptomatic peripheral vascular disease, who were taking a stable dose of simvastatin 20 mg/day for 6 weeks with good compliance	N=93 6 weeks	Primary: Percentage change from baseline in LDL-C; proportion of patients who achieved an LDL-C goal <100 mg/dL Secondary: Safety	Primary: Combination therapy resulted in significantly greater reductions in LDL-C, TC and TC:HDL-C (P<0.01 for all); and significantly more patients treated with combination therapy achieved the LDL-C goal <100 mg/dL (P<0.01). Secondary: There was no significant difference in the proportion of patients who reported adverse events between the two treatments (P=0.606). No significant differences between groups were observed in the number and rate of drug related adverse events, which were reported in 9.8 and 6.3% of patients treated with combination therapy and simvastatin 40 mg (P=0.500). There were few discontinuations due to treatment-related adverse events.
Farnier et al.[259] (2009) IN-CROSS Ezetimibe-simvastatin 10-20 mg/day vs rosuvastatin 10 mg/day	AC, DB, MC, PG, RCT Patients 18 to 80 years of age with hypercholesterolemia (LDL-C ≥100 and ≤190 mg/dL) and high cardiovascular risk who were taking a stable dose of none of the following statin medications for ≥6 weeks prior to trial randomization: atorvastatin (10 or 20 mg), fluvastatin	N=618 6 weeks	Primary: Percent change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG and apo B; proportion of patients achieving LDL-C <100 and <70 mg/dL Secondary: Adverse events	Primary: Combination therapy achieved greater reductions in LDL-C (27.7 vs 16.9%; P≤0.001), TC (17.5 vs 10.3%; P≤0.001), non-HDL-C (23.4 vs 14.0%; P≤0.001) and apo B (17.9 vs 9.8%; P≤0.001) compared to rosuvastatin. Both treatments achieved similar increases in HDL-C (2.1 vs 3.0%; P=0.433) and decreases in TG (11.0 vs 5.3%; P=0.056). A significantly greater proportion of patients receiving combination therapy achieved an LDL-C <100 (73 vs 56%) and <70 mg/dL (25 vs 11%) (P≤0.001 for both). Secondary: There were no between-group differences in the incidences of adverse events or liver transaminase and CK elevations (P values not reported).

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	(80 mg), pravastatin (40 mg), rosuvastatin (5 mg) or simvastatin (20 or 40 mg)			
Viigimaa et al.[260] (2010) Ezetimibe-simvastatin 10-20 mg/day vs rosuvastatin 10 mg/day	Post hoc analysis Patients 18 to 80 years of age with hypercholesterolemia (LDL-C ≥100 and ≤190 mg/dL) and high cardiovascular risk who were taking a stable dose of none of the following statin medications for ≥6 weeks prior to trial randomization: atorvastatin (10 or 20 mg), fluvastatin (80 mg), pravastatin (40 mg), rosuvastatin (5 mg) or simvastatin (20 or 40 mg)	N=618 6 weeks	Primary: Changes from baseline in lipid parameters stratified by statin potency prior to randomization; proportion of patients achieving LDL-C <100, <77 or <70 mg/dL; non-HDL-C <130 or <100 mg/dL; apo B <90 or <80 mg/dL and LDL-C <100 mg/dL, non-HDL-C <130 mg/dL and apo B <90 mg/dL Secondary: Not reported	Primary: Significant treatment-by-subgroup interaction occurred for LDL-C (P=0.013), TC (P=0.025), non-HDL-C (P=0.032) and apo B (P=0.016) with greater between-treatment differences in favor of combination therapy observed in patients who were previously treated with a high potency statin vs a low potency. Individual and triple target attainment was higher with combination therapy compared to rosuvastatin in patients previously treated with a high or low potency statin (P values not reported). Secondary: Not reported
Catapano et al.[261] (2006) Ezetimibe-simvastatin 10-	DB, MC, PG, RCT Patients 18 to 81 years of age with LDL-C ≥145 and	N=2,959 6 weeks	Primary: Percent change from baseline in LDL-C	Primary: At all doses, combination therapy significantly reduced LDL-C compared to rosuvastatin (52 to 61 vs 56 to 57%; P≤0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
20, 10-40 or 10-80 mg/day vs rosuvastatin 10, 20 or 40 mg/day	≤250 mg/dL; TG ≤350 mg/dL; ALT, AST and CK level <1.5 times the upper limit of normal, serum creatinine ≤1.5 mg/dL and HbA_{1c} <9.0% in patients with diabetes		Secondary: Percent changes from baseline in LDL-C at various dose comparisons, HDL-C, TC, apo B, TG, non-HDL-C, LDL-C:HDL-C, TC:HDL-C and hsCRP; proportion of patients who achieved an LDL-C goal <100, <130 or <160 mg/dL; safety	Significantly greater reductions in LDL-C with combination therapy were achieved with the 10/20 (P<0.001), 10/40 (P=0.001) and 10/80 mg (P<0.001) compared to rosuvastatin. Combination therapy produced significantly greater reductions in TC (P<0.001), non-HDL-C (P<0.001), all lipid ratios (P≤0.003), TG (P<0.001) and apo B (P<0.05) compared to rosuvastatin. Increases in HDL-C and decreases in hsCRP were similar between the two treatments (P values not reported). Significantly greater proportions of all patients (P<0.001) and high risk patients (P≤0.005) attained an LDL-C goal <70 mg/dL with combination therapy compared to rosuvastatin across all doses. Safety profiles were comparable between the two treatments. The percent of patients with proteinuria was significantly higher with rosuvastatin compared to combination therapy at doses of 10 vs 10/20 mg (P=0.004) and 40 vs 10/80 mg (P<0.001).
Roeters van Lennep et al.[262] (2008) EASEGO Ezetimibe-simvastatin (EZE/SIMVA) 10-20 mg QD vs doubling of statin dose (atorvastatin 20 mg or simvastatin 40 mg) QD	RCT, OL Patients >18 years of age with controlled stable type 2 diabetes mellitus (>3 months) and/or established coronary heart disease who were on a stable daily statin dose of either atorvastatin 10 mg or simvastatin 20 mg for ≥4 weeks. Entry lipid values	N=367 15 weeks	Primary: Percentages of patients reaching the ESC goal LDL-C <97 mg/dl Secondary: TC, TG, HDL-C, apo-B, and TC/HDL-C	Primary: Overall, the LDL-C target of <97 mg/dl was achieved in 67% of the patients in the EZE/SIMVA group and 26% of the patients in the doubling statin group. After doubling the simvastatin dose from 20 to 40 mg, 24% of patients achieved LDL-C <97 mg/dl. After switching to EZE/SIMVA, 73% of patients reached LDL-C <97 mg/dl (P<0.0001). After doubling the atorvastatin dose from 10 to 20 mg, 28% of patients achieved LDL-C <97 mg/dl. After switching to EZE/SIMVA, 57% of patients achieved LDL-C 97 mg/dl (P<0.0004). After doubling the statin dose, LDL-C <77 mg/dl was achieved in 3% of patients and in 30% of the patients receiving EZE/SIMVA. Secondary: The mean percent change in TC, TC/HDL‑C and apo-B were -6.6%, -6.1% and -7.2%, respectively after doubling the statin dose compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Patients were randomized to continuation of statin monotherapy at a double dose or to EZE/SIMVA	while on statin monotherapy were: LDL-C 97 to 193 mg/dL, TG ≤354 mg/dL and TC ≤270 mg/dL			-17.7%, -13.5%, and -19.7%, respectively in the EZE/SIMVA group (all, P<0.001). HDL-C increased 1.0% after doubling the statin dose compared to -2.6% in the EZE/SIMVA group (P=0.02). There was no significant difference in TG among the treatment groups. There were no significant differences between the treatment groups in adverse events.
Reckless et al.[263] (2008) Ezetimibe-simvastatin (EZE/SIMVA) 10-40 mg QD vs existing statin therapy (with the dose doubled) administered QD	AC, MC, OL, PG, RCT Patients ≥18 years of age hospitalized for an acute coronary event and taking a stable daily dose of one of the following statin medications for ≥6 weeks: atorvastatin (10-40 mg), fluvastatin (20-40 mg), lovastatin (10-20 mg), pravastatin (10-20 mg), rosuvastatin (10-20 mg), or simvastatin (10-40 mg)	N=424 12 weeks	Primary: Absolute LDL-C value at study end point Secondary: TC, TG, HDL-C, non-HDL-C, LDL-C:HDL-C ratio, TC:HDL-C ratio, apo B, CRP, percentages of patients in each treatment group achieving LDL-C ≤100 mg/dL, <77 mg/dL and <70 mg/dL	Primary: Treatment with EZE/SIMVA lowered LDL-C by -25.5 mg/dL (27%) compared to -6.6 mg/dL (4.2%) in the statin group (P≤0.001). The absolute LDL-C value at study end point was 65.7 mg/dL in the EZE/SIMVA group and 85.8 mg/dL in the statin group. Secondary: A greater proportion of patients in the EZE/SIMVA group compared to placebo achieved LDL-C concentrations <100 mg/dL (85.8% vs 72.4%, respectively; P≤0.001), <77 mg/dL (70.1% vs 41.7%, respectively; P≤0.001) and <70 mg/dL (59.8 vs 30.7%, respectively; P≤0.001). Switching to EZE/SIMVA lowered TC by -24.0 mg/dL (14.6%) compared to -5.4 mg/dL (1.7%) in the statin group (P≤0.001). Treatment with EZE/SIMVA produced greater reductions in non- HDL-C (P≤0.001), apo B (P≤0.001), LDL-C/HDL-C (P≤0.001) and TC/HDL-C (P≤0.001) compared to the statin group. Both treatments reduced TG and CRP, and increased HDL-C to a similar extent (P≥0.160 for all). There were no significant differences in adverse events between the two treatment groups.
Fazio et al.[264] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2 g/day	DB, MC, RCT Patients 18 to 79 years of age with hyperlipidemia (Types IIa and IIb) with LDL-C 130 to 190 mg/dL, TG	N=942 64 weeks	Primary: Safety and tolerability of ezetimibe-simvastatin plus niacin ER Secondary:	Primary: The most frequent reason for discontinuation was clinical adverse events related to niacin-associated flushing with ezetimibe/simvastatin plus niacin (0.7% for ezetimibe-simvastatin vs 10.3% for ezetimibe/simvastatin plus niacin). A significant number of patients receiving ezetimibe/simvastatin plus niacin discontinued because of low LDL-C levels <50 mg/dL (1.5 vs 7.1%). The overall incidence of clinical adverse events was slightly greater for

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vs niacin ER 2 g/day vs ezetimibe-simvastatin 10-20 mg/day At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.	≤500 mg/dL, creatinine <2 mg/dL, creatine kinase ≤2 times the upper limit of normal, transaminases ≤1.5 times the upper limit of normal and HbA_{1c} ≤8%		Changes in HDL-C, TG, non-HDL-C and LDL-C	ezetimibe-simvastatin plus niacin compared to ezetimibe-simvastatin owing to the greater number of patients who experienced drug-related clinical adverse events and drug-related discontinuations with ezetimibe-simvastatin plus niacin, mainly attributed to niacin-associated flushing and pruritis. The percentage of patients with consecutive elevations in ALT or AST of at least three times or greater the upper limit of normal, and creatine kinase of at least ten times or greater the upper limit of normal were low and comparable between treatments. A total of 19 patients had adverse events of increased FPG levels, with eight receiving ezetimibe/simvastatin and 11 receiving ezetimibe-simvastatin plus niacin. Secondary: Ezetimibe-simvastatin plus niacin significantly improved baseline HDL-C, TG, non-HDL-C, LDL-C, apo B, apo AI and Lp ratios compared to ezetimibe-simvastatin at week 64 (P<0.004). The changes in TC were comparable between the two treatment groups and the reduction in hsCRP was numerically greater with ezetimibe-simvastatin plus niacin (P value not reported). Ezetimibe-simvastatin plus niacin increased HDL-C considerably during the first 16 weeks of treatment, and at a lower, but significant, rate from 16 to 24 weeks, and then remained constant throughout 64 weeks. The HDL-C change was significantly greater with ezetimibe-simvastatin plus niacin vs ezetimibe/simvastatin throughout the 64 weeks (P<0.001). The reductions in LDL-C, non-HDL-C and TG observed after four weeks with ezetimibe-simvastatin plus niacin were maintained throughout the 64 weeks. In contrast, the levels remained relatively stable with ezetimibe-simvastatin throughout the 64 weeks (P<0.001) and became significant for non-HDL-C after eight weeks (P=0.002) and LDL-C after 12 weeks (P<0.001).
Fazio et al.[265] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2	Subgroup analysis Hyperlipidemic patients with diabetes mellitus, metabolic syndrome without	N=765 at 24 weeks N=574 at 64 weeks	Primary: Changes in HDL-C, TG, non-HDL-C, LDL-C, fasting glucose and uric acid	Primary: The effect of triple therapy on efficacy variables across patient subgroups was generally consistent with the significantly greater improvements observed in the total population compared to niacin and combination therapy. Triple therapy improved levels of LDL-C, other lipids and Lp ratios compared to niacin and combination therapy at 24 and 64 weeks. Triple therapy also increased HDL-C and Lp(a) comparably to niacin and more than combination

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
g/day vs niacin ER 2 g/day vs ezetimibe-simvastatin 10-20 mg/day At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.	diabetes mellitus or neither		Secondary: Not reported	therapy. Triple therapy also decreased hsCRP more effectively than niacin and comparably to combination therapy. Fasting glucose trended higher for niacin compared to combination therapy. Glucose elevations from baseline to 12 weeks were highest for patients with diabetes (niacin, 24.9 mg/dL; triple therapy, 21.2 mg/dL and combination therapy, 17.5 mg/dL). Fasting glucose levels then declined to pretreatment levels at 64 weeks in all subgroups. New onset diabetes was more frequent among patients with metabolic syndrome than those without for the first 24 weeks and trended higher among those receiving niacin (niacin, 5.1%; combination therapy, 1.7% and triple therapy, 8.8%). Between weeks 24 and 64, five and one additional patient(s) receiving combination (cumulative incidence, 5.9%) and triple therapy (cumulative incidence, 9.2%) were diagnosed with diabetes. Treatment-incident increases in uric acid were higher among patients receiving niacin, but there were no effects on symptomatic gout. Secondary: Not reported
Sharma et al.[266] (2006) Niacin ER-lovastatin 1,500-20 mg/day, combination entity, titrated up to LDL-C goal	MC, OL Patients with HTN and dyslipidemia	N=131 24 weeks	Primary: Percent change from baseline in LDL-C, HDL-C, TG, TC Secondary: Not reported	Primary: Niacin ER-lovastatin therapy was associated with a statistically significant reduction from baseline in LDL-C (38%), TG (21%), and TC (25.2%) at week 24 of therapy (P<0.01). Niacin ER-lovastatin therapy was associated with a statistically significant increase from baseline in HDL-C at week 24 of therapy (18.2%; P<0.01). Secondary: Not reported
Karas et al.[267] (2008) OCEANS <u>Group A:</u> Niacin ER-	AC, MC, OL, PG, Phase III, RCT Patients ≥21 years of age with a diagnosis of	N=641 24 weeks	Primary: Group A: mean percent change in non-HDL-C Group B: non-	Primary: In Group A, the mean percent changes in non-HDL-C at 24 weeks were significantly greater with niacin ER/simvastatin 1,000/20 and 2,000/20 mg than with simvastatin 20 mg (-13.6 and -19.5 vs -5.0%, respectively; P<0.05). In Group B, the mean percent change in non-HDL-C at 24 weeks with niacin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 2,000-20 or 1,000-20 mg/day vs simvastatin 20 mg/day <u>Group B:</u> Niacin ER-simvastatin 1,000-40 or 2,000-40 mg/day vs simvastatin 80 mg/day All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing. All patients were instructed to take aspirin or ibuprofen to minimize flushing.	primary type II hyperlipidemia or mixed dyslipidemia, proof of reasonable compliance with a standard cholesterol lowering diet for 4 weeks before screening and for the duration of the trial, and LDL and/or non-HDL levels above normal		inferiority of niacin ER/simvastatin 2,000/40 mg to simvastatin 80 mg in mean percent change in non-HDL Secondary: Mean percent change in LDL-C, TG and HDL-C	ER/simvastatin 2,000/40 mg was non-inferior to that of simvastatin 80 mg (-7.6 vs -6.0%; 95% CI, -7.7 to 4.5). Similar results were obtained in non-inferiority comparisons between niacin ER/simvastatin 1,000/40 mg and simvastatin 80 mg (-6.7 vs -6.0%; 95% CI, -6.6 to 5.3). Secondary: In Group A, the mean percent change in LDL-C at 24 weeks with niacin ER/simvastatin 1,000/20 and 2,000/20 mg were non-superior to simvastatin 20 mg (-11.9 and -14.3 vs -6.7%, respectively) (P value not provided). However, mean percent reduction in TG and mean percent increase in HDL-C with niacin ER/simvastatin 1,000/20 and 2,000/20 mg were “superior” to simvastatin 20 mg (TG, -26.5 and -38 vs -15.3%, respectively, HDL, 20.7 and 29% vs 7.8%, respectively) (P values not provided).
Ballantyne et al.[268]	AC, DB, MC, RCT	N=319	Primary: Percentage	Primary: Combination therapy achieved significant improvements in non-HDL-C.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2008) SEACOAST I Niacin ER-simvastatin 1,000-20 or 2,000-20 mg/day vs simvastatin 20 mg/day All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing.	High risk patients with primary or mixed dyslipidemia	24 weeks	change from baseline in non-HDL-C Secondary: Percent change from baseline in LDL-C, HDL-C, TC/HDL-C, TG, apo B and apo AI	Median change from baseline at week 24 in non-HDL-C was -13.9, -22.5 (P<0.01) and -7.4% (P<0.001) for niacin ER-simvastatin 1,000-20 mg/day, niacin ER-simvastatin 2,000-20 mg/day and simvastatin. Secondary: Combination therapy was associated with nonsignificant additional decreases in LDL-C compared to simvastatin. Both combination therapy regimens had significantly greater decreases in TG, Lp(a), apo B and TC:HDL-C (P values not reported). Combination therapy also achieved significant increases in HDL-C and apo AI/apo B.
Ballantyne et al.[269] (2008) SEACOAST II Niacin ER-simvastatin (NER/S) 2,000-40 mg QD vs niacin ER-simvastatin (NER/S) 1,000-40 mg QD	AC, DB, MC, RCT Men and women ≥21 years of age, compliant with standard cholesterol-lowering diet for ≥4 weeks prior to screening; non-HDL cholesterol ≥130 mg/dL (CHD or CHD risk equivalent), ≥160 mg/dL (≥2 risk factors), ≥190	N=343 24 weeks	Primary: Percent change from baseline to week 24 in non-HDL-C Secondary: Percent change from baseline to week 24 in LDL-C, HDL-C, TC:HDL-C ratio, TG, Lp(a), apoB, and apoAI	Primary: Percent changes from baseline to week 24 in non-HDL-C in both NER/S groups were non-inferior to the simvastatin 80 mg/day group. Median changes in non-HDL-C were -10.1% for simvastatin 80 mg, -11.3% for NER/S 1,000-40 mg, and -17.1% for NER/S 2,000-40 mg. Secondary: Both NER/S treatment groups significantly reduced TG, Lp(a), and TC:HDL-C ratio, and significantly increased HDL-C and apoAI levels compared to patients receiving simvastatin 80 mg (P<0.01 and P<0.001). No significant differences in LDL-C or apoB were noted between the three treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs simvastatin 20 mg/day All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing.	mg/dL (0 to 1 risk factors)			
Charland et al.[270] (2010) High potency dyslipidemia pharmacotherapy (niacin ER-lovastatin, niacin ER-simvastatin, rosuvastatin and ezetimibe/simvastatin	MA (120 unique reports) Patients with hyperlipidemia	N=43,974 Duration varied (≥4 weeks)	Primary: Percent change from baseline in lipid parameters, cardiovascular events Secondary: Not reported	Primary: All of the high potency therapies lowered LDL-C by ≥45%, with the higher doses of ezetimibe/simvastatin and rosuvastatin achieving the greatest LDL-C reduction of -60 and -54%, respectively. In general, percent lipid changes for ezetimibe/simvastatin and rosuvastatin increased in a significant dose dependent manner for TC and LDL-C. With niacin-containing therapies, percent changes in these parameters were flat, and no significant differences between moderate and high doses were observed. Ezetimibe/simvastatin and rosuvastatin did not demonstrate a significant difference in percent change in HDL-C throughout the doses evaluated. Non-niacin-containing therapies appeared to have a flat dose response curve, with weighted percent HDL-C changes between 5 and 9%. Niacin-containing therapies achieved a significant dose response effect. There was no significant difference in percent change in TG with any dose for ezetimibe/simvastatin or rosuvastatin (5, 20 and 40 mg/day). Niacin-containing therapies also demonstrated greater weighted percent changes in TG lowering (-40%) compared to ezetimibe/simvastatin or rosuvastatin (-31 and -24%). In evaluating percent changes in TC between the therapies there was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				significant difference between rosuvastatin 40 mg, ezetimibe/simvastatin 10/80 mg and niacin ER/simvastatin. For LDL-C, there were significant differences between many of the therapies at various doses of rosuvastatin, ezetimibe/simvastatin, niacin ER/lovastatin and niacin ER/simvastatin; however, there was no significant difference in percent change in LDL-C between rosuvastatin 40 mg, ezetimibe/simvastatin 10/40 or 10/80 mg or niacin ER/simvastatin 2,000/40 mg. All of the high-potency therapies are predicted to reduce cardiovascular event rates by >50%, except for the lowest dose of ezetimibe/simvastatin (10/10 mg) and niacin ER/lovastatin (500/20 mg). There was no significant difference in predicted event risk reduction between the largest dose of niacin ER/lovastatin (2,000/40 mg) and niacin ER/simvastatin (2,000/40 mg); however, there was a significant difference in predicted event reduction between either of the highest doses of niacin ER/lovastatin (2,000/40 mg) and niacin ER/simvastatin (2,000/40 mg) compared to all of the doses of rosuvastatin or ezetimibe/simvastatin. The average percent cardiovascular event reduction for ezetimibe/simvastatin, rosuvastatin, niacin ER/lovastatin and niacin ER/simvastatin was 60, 58, 61 and 72%, respectively. Secondary: Not reported
Prevention of Coronary Heart Disease (Combination Products)				
Murphy et al.[271] (2016) IMPROVE-IT Simvastatin 40 mg plus placebo vs combination of ezetimibe 10 mg, plus simvastatin, 40 mg once daily	DB, RCT Patients ≥50 years of age who were hospitalized for an ACS within the preceding 10 days, with either acute MI with or without electrocardiographic ST-segment elevation, or high-risk unstable angina; LDL-C	N=18,144 Median of 6 years	Primary: Composite of time to first CV death, nonfatal MI, unstable angina requiring hospitalization, coronary revascularization (≥30 days post-randomization), or nonfatal	Primary: Among 18,144 patients, there were 9,545 total primary endpoint events (56% were first events and 44% subsequent events). Total primary endpoint events were significantly reduced by 9% with ezetimibe/simvastatin vs placebo/simvastatin (RR, 0.91; 95% CI, 0.85 to 0.97; P=0.007). The reduction in total events was driven by decreases in total nonfatal MI (RR, 0.87; 95% CI, 0.79 to 0.96; P=0.004) and total nonfatal stroke (RR, 0.77; 95% CI, 0.65 to 0.93; P=0.005). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Given in addition to standard ACS therapy. Simvastatin dose was increased in each group to 80 mg if LDL-C was >79 mg/dL	concentration of ≥50 mg/dL, with a maximum of 125 mg/dl if not receiving chronic lipid-lowering therapy, or ≤100 mg/dL if chronically treated		stroke Secondary: Not reported	
Adverse Events				
Newman et al.[272] (2006) Atorvastatin 10 or 80 mg QD vs placebo	MA (42 trials) Patients with various cardiovascular risks, LDL-C ≥130 mg/dL and TG ≤600 mg/dL	N=14,236 2 weeks to 52 months	Primary: Adverse effects Secondary: Not reported	Primary: Treatment-related side effects were similar between treatments (P value not reported). Treatment-associated myalgia was observed in 1.4, 1.5 and 0.7% of patients receiving atorvastatin 10 mg, 80 mg and placebo, respectively (P value not reported). No cases of rhabdomyolysis were reported with atorvastatin or placebo (P value not reported). Elevations in hepatic transaminases at least three times the upper limit of normal were observed in 0.1, 0.6 and 0.2% of patients receiving atorvastatin 10 mg, 80 mg and placebo, respectively (P value not reported). Secondary: Not reported
Everett et al.[273] (2014) JUPITER Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL,	N=17,802 (LDL-C <30 mg/dL (N=767) or ≥70% LDL-C reduction (N=718)) 1.9 years (maximum, 5 years)	Primary: Adverse events Secondary: Not reported	Primary: In the participants who achieved LDL-C <30 mg/dL, the adjusted risk of the composite outcome of any adverse event was higher than in those assigned to active therapy with LDL-C ≥30 mg/dL. No difference was seen by LDL-C reduction ≥70% or <70%. The rate of musculoskeletal disorders was similar for rosuvastatin-treated patients, regardless of achieved LDL-C <30 or ≥30 mg/dL. However, compared with the placebo-treated group, musculoskeletal disorders were more common in each of the rosuvastatin-treated groups. Although the incidence of hepatobiliary disorders was low in each of the achieved LDL-C groups, we observed a statistically significant increase in the risk for those with LDL-C <30 mg/dL compared with rosuvastatin-treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	hsCRP ≥2 mg/L and TG <500 mg/dL treated to very low LDL-C levels (either an LDL-C <30 mg/dL or an LDL-C reduction of ≥70% from baseline)			patients with LDL-C ≥30 mg/dL and compared with those allocated to placebo. We observed a statistically significant increase in the risk of type 2 diabetes for patients with LDL-C <30 mg/dL compared with either rosuvastatin-treated patients with LDL-C ≥30 mg/dL (HR, 1.56; 95% CI, 1.09 to 2.23; P=0.01) or placebo (HR, 1.90; 95% CI, 1.34 to 2.68; P=0.0003). In patients taking rosuvastatin, the rates of renal and urinary disorders were significantly higher in patients with LDL-C <30 vs ≥30 mg/dL (HR, 1.51; 95% CI, 1.21 to 1.90; P=0.0003). The patients on rosuvastatin who met the LDL-C goal of <30 mg/dL appeared to be at increased risk of both measures of hematuria compared with placebo.
Shepherd et al.[274] (2003) Rosuvastatin 5 to 40 mg QD vs atorvastatin 10 to 80 mg QD vs simvastatin 10 to 80 mg QD vs pravastatin 10 to 40 mg QD vs placebo	MA (33 RCTs) Patients with dyslipidemia	N=16,876 25,670 patient-years	Primary: Adverse events, elevation in transaminases, CK, myopathy, dipstick-positive proteinuria, estimated glomerular rate Secondary: Not reported	Primary: The incidence of adverse events was similar with rosuvastatin and placebo (52.1 vs 51.8%, respectively; P value not reported). The incidence of adverse events was similar across all the active treatments (P value not reported). The incidence of elevation in transaminases and CK, myopathy, dipstick-positive proteinuria and estimated glomerular rate was similar across all the active treatment groups (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Silva et al.[275] (2006) Statins (atorvastatin, pravastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin) vs placebo	MA (18 PRO, RCTs) Patients receiving statin therapy or placebo	N=71,108 Up to 317 weeks	Primary: Adverse events, cardiovascular events Secondary: Not reported	Primary: Statin therapy significantly increased the risk of any adverse events by 39% compared to placebo (OR, 1.4; 95% CI, 1.09 to 1.80; P=0.008). Consequently, out of 197 statin-treated patients, one patient would experience an adverse event (95% CI, 24 to 37; P value not reported). Statin therapy was associated with a significant 26% reduction in the risk of a clinical cardiovascular event compared to placebo (OR, 0.74; 95% CI, 0.69 to 0.80; P<0.001). Consequently, the NNT to prevent one additional cardiovascular event was 27. Rosuvastatin trials were not included in the analysis of cardiovascular risk reduction due to inadequate data. The incidence of adverse effects during statin administration was observed in the following order, from highest to lowest: atorvastatin >pravastatin=simvastatin=lovastatin>fluvastatin. Secondary: Not reported
Kashani et al.[276] (2006) Statins (atorvastatin 20 to 80 mg/day, fluvastatin 2.5 to 80 mg/day, lovastatin 10 to 80 mg/day, pravastatin 10 to 160 mg/day, rosuvastatin 1 to 80 mg/day, simvastatin 2.5 to 80 mg/day) vs	MA (35 DB, RCTs) Patients ≥18 years of age with hyperlipidemia	N=74,102 Up to 65 months	Primary: Adverse events (myalgia, CK elevation, rhabdo-myolysis, transaminase elevation), discontinuation due to adverse event Secondary: Not reported	Primary: Statin therapy was associated with a nonsignificant increase in the risk of myalgias (risk difference, 2.7; 95% CI, -3.2 to 8.7; P=0.37), CK elevation (risk difference, 0.2; 95% CI, -0.6 to 0.9; P=0.64), rhabdomyolysis (risk difference, 0.4; 95% CI, -0.1 to 0.9; P=0.13) or discontinuation due to adverse events (risk difference, -0.5; 95% CI, -4.3 to 3.3; P=0.80) compared to placebo. Statin therapy was associated with a significant risk of transaminase elevations (risk difference, 4.2; 95% CI, 1.5 to 6.9; P<0.01) compared to placebo. When individual statins were compared to placebo, atorvastatin was the only statin with a significant increase in the risk of myalgias (P=0.04). When individual statins were compared to placebo, fluvastatin (P<0.01) and lovastatin (P=0.05) were the only statins with a significant increase in the risk of transaminase elevations. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo				
McClure et al.[277] (2007) Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin), stratified by ≤40 mg and >40 mg/day lovastatin equivalent dose vs placebo	MA (119 DB, RCTs) Patients ≥18 years of age with hyperlipidemia	N=86,000 Up to 65 months	Primary: Adverse events (myalgia, myositis, rhabdo-myolysis), discontinuations due to adverse events Secondary: Not reported	Primary: Statin therapy was associated with a nonsignificant increase in the risk of myalgias (OR, 1.09; 95% CI, 0.97 to 1.23; P=0.471), rhabdomyolysis (OR, 1.59; 95% CI, 0.54 to 4.70; P=0.544) or myositis (OR, 2.56; 95% CI, 1.12 to 5.85; P=0.987) compared to placebo. Statin therapy was associated with a significantly lower incidence of discontinuations due to adverse events (OR, 0.88; 95% CI, 0.84 to 0.93; P<0.001) compared to placebo. Secondary: Not reported
Law et al.[278] (2006) Statins (lovastatin, atorvastatin, pravastatin, simvastatin, fluvastatin) vs placebo	SR (2 cohort studies and 21 PC, RCTs) Patients receiving statin therapy or placebo	N=not reported Up to 6.1 years	Primary: Incidence of rhabdomyolysis, myopathy, renal failure, elevated ALT, renal failure, proteinuria, and peripheral neuropathy Secondary: Not reported	Primary: The incidence of rhabdomyolysis associated with the use of statins in two cohort and RCTs was 3.4 (95% CI, 1.6 to 6.5) per 100,000 patient-years (P value not reported). The incidence of rhabdomyolysis associated with the use of statins in addition to gemfibrozil in two cohort studies was 35 (95% CI, 1 to 194) per 100,000 patient-years (P value not reported). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately four times higher in patients receiving lovastatin, simvastatin or atorvastatin compared to those receiving fluvastatin or pravastatin (P<0.001). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 15 times higher in patients receiving statins in combination with gemfibrozil (21 per 100,000 patient-years; 95% CI, 17 to 25)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				compared to those receiving statin therapy (0.70 per 100,000 patient-years; 95% CI, 0.62 to 0.79; P<0.001). The incidence of myopathy associated with the statin therapy in RCTs was five (95% CI, -17 to 27) per 100,000 patient-years (P value not reported). The incidence of liver failure associated with statin therapy, reported to the FDA adverse events reporting system, was 0.1 per 100,000 patient-years of use (P value not reported). Statin therapy in patients with elevated ALT would lead to liver disease in less than one person (P value not reported). Statin therapy was not associated with a higher incidence of renal failure or proteinuria compared to placebo (P value not reported). Patients receiving statin therapy have 1.8 odds of experiencing peripheral neuropathy compared to placebo (95% CI, 1.1 to 3.0; P<0.001). Secondary: Not reported
Dale et al.[279] (2007) Intensive statin therapy; hydrophilic (atorvastatin 80 mg/day) and lipophilic statins (simvastatin 40 to 80 mg/day, lovastatin 76 mg/day) vs moderate statin therapy; hydrophilic (atorvastatin 10	MA (9 RCTs) Patients receiving statin therapy	N=21,765 Up to 5 years	Primary: Incidence of elevations in AST, ALT or CK Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant increased risk of AST or ALT elevation compared to the moderate statin therapy (1.5 vs 0.4%; RR, 3.10; 95% CI, 1.72 to 5.58; P=0.002). Intensive statin therapy was associated with a nonsignificant risk of CK elevation compared to the moderate statin therapy (0.10 vs 0.02%; RR, 2.63; 95% CI, 0.88 to 7.85; P=0.89). In a subanalysis of hydrophilic and lipophilic statins, while no cases of CK elevation occurred in the hydrophilic intensive statin group, patients on lipophilic intensive statin therapy experienced a nonsignificant risk in CK elevation (RR, 6.09; 95% CI, 1.36 to 27.35; P≥0.11). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day, pravastatin 40 mg/day) and lipophilic statins (simvastatin 20 to 40 mg/day, lovastatin 4 mg/day)				
Ko. et al.[280] (2013) Intensive statin therapy (atorvastatin ≥40 mg, rosuvastatin ≥20 mg, or simvastatin ≥60 mg) vs moderate statin therapy (atorvastatin <40 mg, rosuvastatin <20 mg, simvastatin <60 mg, and any dosage of fluvastatin, lovastatin, or pravastatin)	RETRO Patients with myocardial infarction aged >65 years old, hospitalized in Ontario, Canada, from 2004 to 2010, only the initial hospitalization in the study period was included in the cohort. Patients with diabetes mellitus and patients who were not prescribed statin medications were excluded	N=17,080 5 years	Primary: New development of diabetes mellitus after hospital discharge Secondary: All-cause mortality and repeat hospitalization for ACS	Primary: At 5 years, after hospitalization with myocardial infarction, 13.6% of patients receiving intensive-dose statins and 13.0% of the patients receiving moderate-dose statins had a new diagnosis of diabetes mellitus (P=0.19). Secondary: At 5 years, the rate of ACS or death was significantly lower at 44.8% in the intensive-dose statin group compared with 46.5% in the moderate-dose statin group (P=0.044). At 5 years, the rate of ACS was significantly lower with intensive-dose statins at 22.2 vs 23.5% compared with moderate-dose statins (P=0.039). Rate of death was not significantly different in the treatment groups (34.8% in both groups) during the study period (P=0.89).
Silva et al.[281] (2007) Intensive statin therapy	MA (4 RCTs) Patients with ACS or stable CAD receiving statins	N=27,548 3.4 years	Primary: CK ≥10 times the upper limit of normal, with or without	Primary: Intensive statin therapy was associated with a significant increased risk of any adverse event compared to moderate statin therapy (OR, 1.44; 95% CI, 1.33 to 1.55; P<0.001). Consequently, out of 30 patients treated with intensive statin therapy, one patient would experience an adverse event (95% CI, 24 to 37; P

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(atorvastatin 80 mg/day, simvastatin 80 mg/day) vs moderate statin therapy (atorvastatin 10 mg/day, simvastatin 20 mg/day, pravastatin 40 mg/day)	for the reduction of secondary cardiovascular events		myalgia; ALT or AST ≥3 times the upper limit of normal; rhabdo-myolysis; drug-induced adverse effects requiring drug discontinuation; any drug-induced adverse event; all-cause mortality; cardiovascular death; nonfatal MI; and stroke Secondary: Not reported	value not reported). Intensive statin therapy was associated with a significant increased risk (absolute risk, 2.14%) of an adverse drug event requiring discontinuation of drug therapy (OR, 1.28; 95% CI, 1.18 to 1.39; P≤0.001). Intensive statin therapy was associated with a significant increased risk (absolute risk, 1.2%) of an elevation in AST and ALT at least three times the upper limit of normal (OR, 4.84; 95% CI, 3.27 to 6.16; P≤0.001). Consequently, out of 86 patients treated with intensive statin therapy, one patient would experience an elevation in AST and ALT at least three times the upper limit of normal (95% CI, 72 to 106; P value not reported). Intensive statin therapy was associated with a significant increased risk (absolute risk, 0.07%) of an elevation in CK ≥10 times the upper limit of normal (OR, 9.97; 95% CI, 1.28 to 77.92; P=0.028). Consequently, out of 1,534 patients treated with intensive statin therapy, one patient would experience an elevation in CK ≥10 times the upper limit of normal (P value not reported). There was no difference in the incidence of rhabdomyolysis between the treatments (P value not reported). Intensive statin therapy was associated with a nonsignificant reduction in all-cause mortality compared to moderate-dose statin therapy (P=0.185). Intensive statin therapy was associated with a significant reduction in the risk for cardiovascular death (P=0.031), nonfatal MI (P<0.001) and stroke (P=0.004). Consequently, the NNT to prevent one additional cardiovascular death, MI or stroke was 229, 99 and 166, respectively. Secondary: Not reported
Strony et al.[282] (2008) Ezetimibe 10 mg QD	Pooled analysis of 2 ES, MC, OL Patients with primary	N=795 12 to 15 months	Primary: Tolerability Secondary: LDL-C, HDL-	Primary: Treatment-emergent adverse events were reported in 81% of patients receiving ezetimibe plus pravastatin (15 months) and in 84% of patients receiving ezetimibe plus simvastatin (12 months).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
coadministered with either pravastatin 10 to 40 mg QD or simvastatin 10 to 80 mg QD	hypercholesterolemia		C, TG, TC, and proportion of patients achieving LDL-C goal	The most commonly reported treatment-emergent adverse events were upper respiratory tract infection (18%), headache (11%), musculoskeletal pain (10%), arthralgia (10%), sinusitis (10%), abdominal pain (8%), bronchitis (6%), coughing (6%), nausea (6%), back pain (5%), myalgia (5%), chest pain (5%), and fatigue (5%) with ezetimibe plus pravastatin. The most commonly reported treatment-emergent adverse events were upper respiratory tract infection (19%), arthralgia (11 %), musculoskeletal pain (10%), headache (9%), back pain (8%), myalgia (8%), abdominal pain (7%), nausea (7%), pharyngitis (6%), coughing (5%), fatigue (5%), and urinary tract infection (19%) with ezetimibe plus simvastatin. During the ezetimibe plus pravastatin extension study, 7% experienced serious adverse events. During the ezetimibe plus simvastatin extension study, serious adverse events were reported in 10% of patients. Life-threatening adverse events were reported in four patients in the ezetimibe plus simvastatin study. The incidence of newly reported adverse events did not increase over time in either study. In the ezetimibe plus pravastatin study, 1% of patients experienced increases in ALT/AST >3 X upper limit or normal, whereas this was not reported in the patients receiving ezetimibe plus simvastatin. Secondary: The mean LDL-C was reduced by 36.5 and 40.4% in the ezetimibe plus pravastatin and ezetimibe plus simvastatin studies, respectively. Similar reductions in TC and TG, and an increase in HDL-C, were achieved and maintained throughout the study period in both studies. In the ezetimibe plus pravastatin study, 85% of patients achieved their NCEP ATP III LDL-C goal and 80% of patients in the ezetimibe plus simvastatin study achieved their recommended goal.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, SR=sustained-release, TID=three times daily; XL=extended-release, XR=extended-release
Study abbreviations: AC=active comparator, DB=double blind, DD=double dummy, ES=extension study, FU=follow-up, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open label, PA=parallel-arm, PC=placebo-controlled, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, XO=cross-over
Miscellaneous abbreviations: ACS=acute coronary syndrome, ALT=alanine aminotransferase, apo=apolipoprotein, ARR=absolute risk reduction, AST=aspartate aminotransferase, BMI=body mass index, BNP=B-type natriuretic peptide, BP=blood pressure, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence

interval, CIMT=carotid intima-media thickness, CK=creatine kinase, CKD=chronic kidney disease, CPK=creatinine phosphokinase, CRP=C-reactive protein, DBP=diastolic blood pressure, ECG=electrocardiogram, eGFR=estimated glomerular filtration rate, FBG=fasting blood glucose, FH=familial hypercholesterolemia, GFR=glomerular filtration rate, HAART=highly active anti-retroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, heFH=heterozygous familial hypercholesterolemia, HIV=human immunodeficiency virus, hoFH=homozygous familial hypercholesterolemia, HOMA=homeostasis model assessment, HR=hazard ratio, hsCRP=high-sensitivity C-reactive protein, HTN=hypertension, IMT=intima-medial thickness, IDL-C=intermediate-density lipoprotein cholesterol, JNC 7=Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program, Adult Treatment Panel, NNT=number needed to treat, NYHA=New York Heart Association, OR=odds ratio, PAD=peripheral arterial disease, PAV=percent atheroma volume, PCI=percutaneous coronary intervention, RR=relative risk, SBP=systolic blood pressure, SE=standard error, STEMI=ST-segment myocardial infarction, TAV=total atheroma volume, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TRL=triglyceride lipoprotein, VLDL-C=very low-density lipoprotein, VTE=venous thromboembolism

Additional Evidence

Dose Simplification

Wongwiwatthananukit et al evaluated the safety and efficacy with rosuvastatin 10 mg administered once-daily compared to every-other-day in patients with primary hypercholesterolemia. There was a significantly larger reduction in low-density lipoprotein cholesterol (LDL-C) with once daily therapy compared to every-other-day administration (48 vs 39%, respectively; P=0.011). Total cholesterol and triglycerides were significantly lower with once daily therapy (P<0.05). However, there was no difference in the percentage of patients achieving their National Cholesterol and Education Program Adult Treatment Panel III LDL-C goals (P=0.18).[283]

LaFleur et al evaluated the differences in adherence and persistence with (1) a fixed-dose combination product containing lovastatin and extended-release niacin, (2) statin monotherapy, (3) extended-release niacin monotherapy, and (4) extended-release niacin taken with lovastatin as separate formulations. A total of 2,389 patients met the eligibility criteria and were followed for one year. All groups exhibited an adherence rate >80%. Patients receiving extended-release niacin and lovastatin taken separately demonstrated higher adherence rates compared to those on the fixed-dose product (90 vs 88%; P=0.033). In addition, patients were less adherent to statin monotherapy than to either the fixed-dose combination product or niacin monotherapy (81, 90, and 89%, respectively; P<0.05). At 12 months, all treatment groups had a persistence rate of <20%. At nine months, patients randomized to niacin monotherapy exhibited a significantly lower rate of persistence compared to the rest of the groups (P<0.05). Since this was an adherence study only, based on an evaluation of pharmacy claims, the study did not measure the impact of adherence on LDL-C or other cholesterol goals.[284]

Balu et al retrospectively evaluated medication adherences rates in patients treated with the fixed-dose combination of niacin extended-release and lovastatin (NERL) compared to the multi-pill combination of niacin extended-release plus lovastatin (NER/L) or simvastatin (NER/S) using an integrated managed care database. Adherence rates were greater among patients initiating therapy with NERL compared to NER/S or NER/L P<0.0001). A higher percentage of patients initiating therapy with NERL (34.2%) exhibited optimal adherence (>80%) compared to those initiating therapy with NER/S (29.6%; P<0.0001) or NER/L (25.9%; P<0.0001). There were fewer cardiovascular disease-associated emergency room visits in patients with optimal adherence initiating therapy with NERL compared to those with optimal adherence initiating therapy with NER/S or NER/L (P=0.003), inpatient visits (P=0.018, outpatient visits (P<0.0001), and prescription fills (P<0.0001). Patients with optimal adherence had an 8% decrease (P=0.023) in annual cardiovascular disease-attributable total medical resource utilization compared to patients with suboptimal adherence (<80%).[285]

Patel et al evaluated adherence rates in patients newly initiated on dual therapy with a calcium channel blocker and a statin (as either a fixed-dose combination product or administration of each component separately). In this six month, retrospective, pharmacy claims database analysis, the authors found that the percentage of patients achieving adherence rates ≥80% were: 67.7% with amlodipine-atorvastatin; 49.9% with amlodipine plus atorvastatin; 40.4% with amlodipine plus other statins; 46.9% with other calcium channel blockers plus atorvastatin; 37.4% with other calcium channel blocker plus other statin (P<0.0001 amlodipine-atorvastatin vs all other cohorts).[286]

Stable Therapy

Cheetham et al evaluated the efficacy and safety of switching patients from Zocor® to generic lovastatin. Patients switching to lovastatin experienced a reduction in LDL-C, an increase in high-density lipoprotein cholesterol and a decrease in triglycerides. Rates of alanine aminotransferase and creatine kinase elevations were not found to be significantly different before or after conversion.[287]

Usher-Smith et al examined the effects of switching patients from atorvastatin to simvastatin in a two year retrospective analysis. Patients initially receiving atorvastatin 10 and 20 mg were converted to simvastatin 10, 20, or 40 mg, respectively. The change in therapy was not associated with a significant alteration in baseline total cholesterol levels (P=0.06).[288]

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 HMG-CoA Reductase Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Atorvastatin	suspension, tablet	Atorvaliq®, Lipitor®*	$$$$$	$
Fluvastatin	capsule, extended-release tablet	Lescol XL®*	$$$$$	$$$$
Lovastatin	extended-release tablet, tablet*	Altoprev®	$$$$$	$
Pitavastatin	tablet	Livalo®, Zypitamag®	$$$$$	N/A
Pravastatin	tablet	N/A	N/A	$
Rosuvastatin	sprinkle capsule, tablet	Ezallor®	$$$$$	$
Simvastatin	tablet	Zocor®*	$$$$$	$
Combination Products				
Amlodipine and atorvastatin	tablet	Caduet®*	$$$$$	$$$
Ezetimibe and simvastatin	tablet	Vytorin®*	$$$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The HMG-CoA reductase inhibitors (statins) are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia (refer to Table 4 for specific indications). The fixed-dose combination products (amlodipine and atorvastatin, and ezetimibe and simvastatin) are indicated for use when dual therapy is appropriate.[1-11] Statins can decrease low-density lipoprotein cholesterol (LDL-C) by 18 to 60% and triglycerides (TG) by 7 to 30%, as well as increase high-density lipoprotein cholesterol (HDL-C) by 5 to 15% when administered as monotherapy.[12-14] Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and fixed-dose amlodipine-atorvastatin and ezetimibe-simvastatin are available in a generic formulation.

In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial

treatment with a statin, a bile acid sequestrant, or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease (CHD) or coronary heart disease equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy. Choice of statin and dose should be based on cost and the amount of lipid lowering required for a specific patient. Patients with risk factors for CHD but no history of disease are likely to decrease their risk of CHD with lipid lowering therapy.[14] Guidelines do not give preference to statin over another.[14-27]

The American College of Cardiology/American Heart Association (ACC/AHA) released guidelines in 2013 which support initiating a statin in patients with established atherosclerotic cardiovascular disease (ASCVD). According to these recommendations, percent reduction in LDL-C is an indicator of response and adherence to therapy, but treating to a targeted level is not a primary goal.[20] Combination therapy can be considered on an individual basis, but studies of combination therapy have generally not shown benefit beyond statin monotherapy. The 2018 American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol recommend using an LDL-C threshold of 70 mg/dL to consider the addition of non-statins to statin therapy in very high-risk ASCVD patients.[19] Additionally, if patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.[20] High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. When high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated.[20] Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy with no 10-year ASCVD risk estimation required: use high-intensity statin therapy unless contraindicated and intensify statin therapy to achieve at least a 50% LDL-C reduction.[20] The ACC/AHA guidelines note that there is no differentiation between the specific statins and doses used in primary- and secondary-prevention trials and that statins reduce ASCVD risk similarly in both populations.[20]

Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, total cholesterol, and TG, as well as positively impact other lipid/lipoprotein parameters. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens.[30-138,241-271] The statins differ in their potency and their effects on LDL-C are dose-dependent. Atorvastatin and rosuvastatin are the most potent agents available and can lower LDL-C by ~60%.[12-16] The 2013 ACC/AHA guidelines recommend selecting statin product and dose based on intensity of LDL-C-lowering effect. Moderate-intensity statins lower LDL-C by 30 to <50% (e.g. atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin 20 to 40 mg, pravastatin 40 mg, lovastatin 40 mg, fluvastatin 40 mg twice daily, and pitavastatin 2 to 4 mg) and high-intensity statins lower LDL-C by ≥50% and include atorvastatin 40 to 80 mg and rosuvastatin 20 to 40 mg.[20] In general, the combination products do not offer any significant clinical advantage over coadministration of their individual components.

The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by one to two percent of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatine kinase. Pravastatin and rosuvastatin do not undergo extensive first-pass metabolism; therefore, they are associated with a lower risk for drug interactions. Atorvastatin, lovastatin, and simvastatin are primarily metabolized by the cytochrome P450 (CYP) 3A4 isoenzyme, while fluvastatin is metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles.[12,13]

There is insufficient evidence to support that one brand HMG-CoA reductase inhibitor 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 HMG-CoA reductase inhibitors 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 HMG-CoA reductase 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of
Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors
AHFS Class 240624
February 7, 2024

I. Overview

Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease produced predominantly in the liver that leads to the degradation of hepatocyte low density lipoprotein (LDL) receptors and increased low density lipoprotein-cholesterol (LDL-C) levels. PCSK9 inhibitors work to inhibit the action of this enzyme leading to a decrease in LDL-C levels by as much as 60% in patients on statin therapy. This reduction in LDL-C may produce clinical benefits such as reductions in myocardial infarction or cardiac death. There are currently two Food and Drug Administration (FDA)-approved PCSK9 inhibitors commercially available. These agents include Praluent® (alirocumab) and Repatha® (evolocumab).[1]

Both Praluent® (alirocumab) and Repatha® (evolocumab) are FDA-approved as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH] and homozygous familial hypercholesterolemia [HoFH]) to reduce LDL-C.[2,3] Praluent® (alirocumab) is also indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. Repatha® (evolocumab) is also indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease. It is also indicated in pediatric patients aged 10 years and older with HeFH or HoFH as adjunctive therapy to other LDL-C lowering therapies.[3]

The American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol was released in 2018. In patients with clinical atherosclerotic cardiovascular disease (ASCVD) who are judged to be very high risk, maximally tolerated LDL-C lowering therapy including maximally tolerated statin therapy and ezetimibe should be utilized before considering PCSK9 inhibitor therapy. It is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost in this patient population when LDL-C is >70 mg/dL despite maximally tolerated LDL-C lowering therapy. Patient preference should be considered in the discussion to initiate PCSK9 inhibitor therapy, including considerations of the patient's perception of net benefit, convenience/burden of additional therapy, cost, quality of life, and the potential to jeopardize adherence to other evidence-based therapies.[5] The 2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis recommend PCSK9 inhibitors be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH and individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.[6]

The PCSK9 inhibitor products 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 2022.

Table 1. PCSK9 Inhibitor Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alirocumab	injection	Praluent®	none
Evolocumab	injection	Repatha®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the treatment of use of PCSK9 inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using PCSK9 Inhibitors

Clinical Guideline	Recommendation(s)
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[4]	Statin treatment • The panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD. • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (ten-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated ten-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated ten-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated ten-year ASCVD risk of 5.0 to <7.5%. • Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based

Clinical Guideline	Recommendation(s)
	treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and non-pregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. • Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. • Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age. • Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. • Creatinine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). • Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g.,

Clinical Guideline	Recommendation(s)
	those who have undergone solid organ transplantation or are receiving treatment for HIV) . A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug). • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C

Clinical Guideline	Recommendation(s)
	reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. • In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. <u>Non statin safety</u> • Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. • Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. • In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. • To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. • Bile acid sequestrants should not be used in individuals with baseline fasting triglyceride (TG) levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe TG elevations might occur. • A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. • It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL.

Clinical Guideline	Recommendation(s)
	• It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. • Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. • Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. • Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. • If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (2018)**[5]	<u>Top 10 messages to reduce risk of atherosclerotic cardiovascular disease through cholesterol management</u> • In all individuals, emphasize a heart-healthy lifestyle across the life course. • In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. ○ Clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin. • In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy. Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. • In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. • In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. • In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels

Clinical Guideline	Recommendation(s)
	≥70 to 189 mg/dL (≥1.8 to 4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium (CAC). • Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement four to 12 weeks after statin initiation or dose adjustment, repeated every three to 12 months as needed. <u>Recommendations for Statin Therapy Use in Patients With ASCVD</u> • In patients who are 75 years of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. • In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels. • In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe. • In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost. • In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy. • In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences. • In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. • In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe. • In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (three to five years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events. <u>Recommendations for primary severe hypercholesterolemia (LDL-C ≥190 mg/dL)</u> • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher, maximally tolerated statin therapy is recommended. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher, ezetimibe therapy is reasonable. • In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL, who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL, while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered. • In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level

Clinical Guideline	Recommendation(s)
	of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. • In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher and who achieve an on-treatment LDL-C level of 130 mg/dL or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. <u>Recommendations for patients with diabetes mellitus</u> • In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. <u>Primary prevention recommendations for adults 40 to 75 years of age with LDL levels 70 to 189 mg/dL</u> • In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more. • For the primary prevention of clinical ASCVD in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL, the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%). • Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision. • In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy. • In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND o If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); o If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥ 55 years of age; o If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy • In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin. • In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Recommendations for older adults</u> • In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL, initiating a moderate-intensity statin may be reasonable. • In adults 75 years of age or older, it may be reasonable to stop statin therapy

Clinical Guideline	Recommendation(s)
	when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy. • In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL, it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy. <u>Recommendations for children and adolescents</u> • In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity. • In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C. • In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL or higher with a clinical presentation consistent with familial hypercholesterolemia (FH) and who do not respond adequately with three to six months of lifestyle therapy, it is reasonable to initiate statin therapy. • In children and adolescents with a family history of either early CVD or significant hypercholesterolemia, it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age two years to detect FH or rare forms of hypercholesterolemia. • In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia. • In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome. • In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of nine and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities. <u>Recommendations for hypertriglyceridemia</u> • In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides. • In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy. • In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy. • In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL, and especially fasting triglycerides ≥1000 mg/dL), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute

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	pancreatitis, fibrate therapy. Recommendations for statin safety and statin-associated side effects • A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully. • In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors. • In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and SAMS, is recommended before initiation of treatment. • In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy. • In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss. • In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity. • In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks. • In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit. • Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS. • In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.
American Association of Clinical Endocrinologists And American College of Endocrinology: **Guidelines For Management Of Dyslipidemia And Prevention Of Cardiovascular Disease (2017)[6] and Executive Summary (2020)[7]**	Cholesterol Goals • For patients at low risk for ASCVD (i.e., no risk factors), goals of LDL-C<130 mg/dL, non-HDL-C<160 mg/dL, and TG<150 mg/dL are recommended. • For patients at moderate risk for ASCVD (i.e., two or fewer risk factors and a calculated 10-year risk of <10%), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at high risk for ASCVD (i.e., two or more risk factors and a 10-year risk between 10% and 20% or who have diabetes or stage ≥3 CKD with no other risk factors), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at very high risk for ASCVD (i.e., established clinical ASCVD or recent hospitalization for ACS, carotid or peripheral vascular disease, or 10-year risk >20%; diabetes with one or more risk factor(s); CKD stage 3 or higher with albuminuria; or HeFH), goals of LDL-C<70 mg/dL, non-HDL-C<100 mg/dL,

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	apo B<80 mg/dL, and TG<150 mg/dL are recommended. • For individuals at extreme risk (i.e., progressive ASCVD including unstable angina that persists after achieving an LDL-C <70 mg/dL; established clinical ASCVD in individuals with diabetes, CKD stage 3 or higher, and/or HeFH); history of premature ASCVD (<55 years of age for males or <65 years of age for females), goals of LDL-C<55 mg/dL, non-HDL-C<80 mg/dL, apo B<70 mg/dL, and TG<150 mg/dL are recommended. • An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100 to 129 mg/dL considered "borderline" and 130 mg/dL or greater considered "high" (based on recommendations from the American Academy of Pediatrics). • Due to its potential cardioprotective role, HDL-C should be >40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C. <u>General Recommendations</u> • A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes and patient education with pharmacotherapy as needed to achieve evidence based targets. • A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include ≥30 minutes of moderate-intensity physical activity [consuming 4 to 7 kcal/min] four to six times weekly, with an expenditure of ≥200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities. • Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs. • In addition to aerobic activity, muscle-strengthening activity is recommended at least two days a week. • For adults, a reduced-calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains (primarily whole grains), fish, and lean meats is recommended. • For adults, the intake of saturated fats, trans-fats, and cholesterol should be limited, while LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10 to 25 g/day). • Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children. • Excessive alcohol intake should be avoided. • Tobacco cessation should be strongly encouraged and facilitated. • In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals. <u>Lipid Lowering Therapy Recommendations</u> • Statins o Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. o Mild elevations in blood glucose levels and/or an increased risk of new-onset type 2 diabetes mellitus associated with intensive statin therapy do

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	not outweigh the benefits of statin therapy for ASCVD risk reduction. ○ In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered. ○ Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes who also have at least one additional risk factor should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL. ○ Extreme-risk individuals should be treated with statins to target an even lower LDL-C treatment goal of <55 mg/dL. • Fibrates ○ Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). ○ Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations are <40 mg/dL. ○ In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add fibrate. ○ In patients treated with a statin and icosapent ethyl with TG≥150 mg/dL, a fibrate may be considered. • Omega-3 Fish Oil ○ Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose. ○ Omega-3 should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. ○ In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add omega-3. • Niacin ○ Niacin therapy is recommended principally as an adjunct for reducing TG. ○ Niacin therapy should not be used in individuals aggressively treated with statin due to absence of additional benefits with well-controlled LDL-C. ○ Niacin should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. ○ In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add niacin. ○ In patients treated with a statin and icosapent ethyl with TG>150 mg/dL, niacin may be considered. • Icosapent Ethyl ○ Icosapent ethyl (two grams twice daily) should be added to a statin in any patient with established ASCVD or diabetes with two or more ASCVD risk factors and triglycerides between 135 to 499 mg/dL to prevent ASCVD events. • Bile Acid Sequestrants ○ Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG. • Cholesterol Absorption Inhibitors ○ Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals. ○ Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk. • PCSK9 Inhibitors

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	○ PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH. ○ PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals. • Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal.
American Heart Association: **The Agenda for Familial Hypercholesterolemia A Scientific Statement From the American Heart Association (2015)[8]**	<u>Treatment of Heterozygous Familial Hypercholesterolemia</u> • For adult heterozygotes, the initial approach to treatment with an initial goal of reducing LDL-C by at least 50%, usually beginning with a statin. • This can be followed by achieving an LDL-C of <100 mg/dL (absence of coronary artery disease (CAD) or other major risk factors) or 70 mg/dL (presence of CAD or other major risk factors). • Ezetimibe or colesevelam is preferred as an additional LDL-C–lowering agent over niacin. • When the statin-induced side effects are disabling but a statin response is present, treatment with a lower dose of a statin given daily or on alternate days may be sufficient, together with other lipid-lowering medications, to reduce LDL-C to reasonably acceptable levels and to limit the disabling side effects. • A combination of ezetimibe, niacin, and bile acid sequestrants may also reduce LDL-C satisfactorily in patients with moderate elevations of LDL-C. • PCSK9 inhibitors have been shown to reduce LDL-C by an additional 50% to 60% on top of high-dose statin with or without ezetimibe in HeFH. • Alternatively, LDL apheresis or new forms of therapy, including microsomal transfer protein inhibitors and apoB antisense oligonucleotides. <u>Treatment of Homozygous Familial Hypercholesterolemia</u> • Lipid-lowering therapy, usually statins, should be instituted at diagnosis and as early as possible. • Statins reduce LDL-C levels modestly in HoFH, even in those who are receptor negative. • The addition of the cholesterol absorption inhibitor ezetimibe to statin therapy has been shown to reduce LDL-C by an additional 10% to 15%. • Other cholesterol-lowering medications such as bile acid sequestrants, niacin, fibrates, and probucol have also been used, but their LDL-C–reducing effects in HoFH are modest. • Mipomersen can reduce LDL-C by an additional 25% in HoFH patients when given subcutaneously in combination with maximum tolerated doses of lipid-lowering therapy, but even the addition of mipomersen does not achieve the recommended LDL-C target in the vast majority of HoFH patients. • Lomitapide can also reduce LDL-C levels by up to by 50% in HoFH patients; however, gastrointestinal side effects and elevation in liver enzymes are common. • PCSK9 inhibitor therapy has recently been shown to be partially effective in HoFH, at least in those subjects who are receptor defective. • Lipoprotein apheresis appears to improve cardiovascular outcomes and should be considered by five years of age or earlier in exceptional circumstances. • Liver transplantation has been described as a treatment for both children and young adults with HoFH in the form of case series.
National Cholesterol Education Program: **Implications of Recent Clinical Trials**	• TLC remains an essential modality in clinical management. • When LDL-C lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of

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for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[9]	cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institute for Health and Clinical Excellence: **Identification and management of familial hypercholesterolemia (2008)[10]** **Last updated October 2019**	<u>Drug treatment in adults</u> • When offering lipid-modifying drug therapy to adults with familial hypercholesterolemia (FH), inform the patient that this treatment should be life-long. • Offer a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who would otherwise be

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	initiated on statin therapy but who are unable to do so because of contraindications or intolerance to initial statin therapy. • Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who have been initiated on statin therapy when: o Serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy AND o Consideration is being given to changing from initial statin therapy to an alternative statin. • Appropriate control of cholesterol concentrations should be based on individualized risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. • Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist center. • Offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). • Offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are at a very high risk of a coronary event [i.e., they have established coronary heart disease, a family history of premature coronary heart disease, or two or more other cardiovascular risk factors (e.g. they are male, they smoke, or they have hypertension or diabetes)]. • Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration. • The decision to offer treatment with a bile acid sequestrant (resin) or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH. • Exercise caution when adding a fibrate to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together. <u>Drug treatment in children and young people</u> • All children and young people diagnosed with, or being investigated for, a diagnosis of FH should have a referral to a specialist with expertise in FH in children and young people. • Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of ten years. The decision to defer or offer lipid-modifying drug therapy to a child or young person should take into account their age, the age of onset of coronary heart disease within the family, and the presence of other cardiovascular risk factors, including LCL-C concentration. • When offering lipid-modifying drug therapy for children or young people, inform the child/young person and their parent/caregiver that this treatment should be life-long. • Offer statins to children with FH by the age of ten years or at the earliest opportunity thereafter. • For children and young people with FH, consider a statin that is licensed for use in the appropriate age group. Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group. • In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in

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	children and young people should consider offering: ○ A higher dose of statin than is licensed for use in the age group, and/or ○ More than one lipid-modifying drug therapy, and/or ○ Lipid-modifying drug therapy before the age of ten years. • In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy, and this should be considered before LDL apheresis. • In children and young people with FH who are intolerant of statins, consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration [such as bile acid sequestrants (resins), fibrates, or ezetimibe]. • Routine monitoring of growth and pubertal development in children and young people with FH is recommended.
American College of Cardiology: **Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2022)**[11]	• Provides recommendations for situations not covered by the 2018 ACC/AHA cholesterol guidelines and for whether or when to use non-statin therapies if response to statins is deemed inadequate. • For all patient groups, lifestyle modification (adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) is a critical component of ASCVD risk reduction. The clinician-patient discussion regarding the addition of a non-statin medication to the current medication regimen should address the potential for net ASCVD risk reduction, safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering, cost, convenience, and medication storage, pill burden, frequency and route of administration, potential to jeopardize adherence to evidence-based therapies and patient preference. <u>Adults With Clinical ASCVD on Statin Therapy for Secondary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider LDL apheresis under care of lipid specialist if baseline LDL-C ≥190 mg/dL not due to secondary causes without clinical or genetic diagnosis of familial hypercholesterolemia. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH under care of lipid specialist, if at very high risk and baseline LDL-C ≥190 mg/dL not due to secondary causes with clinical diagnosis or genetic confirmation of familial hypercholesterolemia. <u>Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Primary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH.
European Atherosclerosis Society/European Society of Vascular Medicine Joint Statement: **Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease (2021)**[12]	• Statins, at the highest tolerated dose, are indicated in patients with PAD for the prevention of cardiovascular events. • LCL-C should be lowered to <1.4 mmol/L and by >50% if pre-treatment values are 1.8 to 3.5 mmol/L. • Combination treatment with a statin and ezetimibe may be considered to improve LDL-C goal attainment. This approach could allow better tolerance of a lower dose of statin in patients with statin side-effects. • A PCSK9 inhibitor should be added if LDL-C levels remain 50% higher than goal despite statin treatment, with or without ezetimibe. • Antiplatelet therapy is indicated to prevent further cardiovascular events. This should either be clopidogrel 75 mg/day or the combination of aspirin 100 mg/day and rivaroxaban. • Dual antiplatelet therapy should be given for at least one month after drug coated balloon angioplasty, and for three months after either drug eluting or

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	covered stent implantation. • Combination therapy with aspirin and rivaroxaban should be considered for dual antiplatelet therapy post-intervention.

III. Indications

The Food and Drug Administration (FDA)-approved indications for PCSK9 inhibitors are noted in Table 3.

Table 3. FDA-Approved Indications for PCSK9 Inhibitors[2,3,13,14]

Indication	Alirocumab	Evolocumab
Adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including HeFH) to reduce low-density lipoprotein cholesterol (LDL-C)	✔	✔
Adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of adults with HoFH who require additional lowering of LDL-cholesterol	✔	✔
To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease	✔	
To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease		✔
Adjunct to diet and other LDL-lowering therapies for the treatment of patients ≥10 years old with HeFH who require additional lowering of LDL-cholesterol		✔
Adjunct to other LDL-C-lowering therapies in patients ≥10 years of age with HoFH who require additional lowering of LDL-cholesterol		✔

HeFH=heterozygous familial hypercholesterolemia, HoFH=homozygous familial hypercholesterolemia

IV. Pharmacokinetics

The pharmacokinetic parameters of PCSK9 inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of PCSK9 Inhibitors[13,14]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (days)
Alirocumab	85	Not reported	Protein degradation	Proteolytic pathway	17 to 20
Evolocumab	72	Not reported	Immunoglobulin clearance pathways	Systemic clearance	11 to 17

V. Drug Interactions

Major drug interactions with the PCSK9 inhibitors are listed in Table 5. The median apparent half-life of alirocumab is reduced to 12 days when administered with a statin, and an approximately 20% decrease in the C_{max} and AUC of evolocumab was observed in patients co-administered with a high-intensity statin regimen. These differences are not clinically meaningful and do not impact dosing recommendations.[2,3,13,14]

Table 5. Major Drug Interactions with PCSK9 Inhibitors[13,14]

Generic Name(s)	Interaction	Mechanism
Evolocumab	Tofacitinib – potent immunosuppressants	Concurrent use of tofacitinib and potent immunosuppressants may result in increased risk of immunosuppression.

VI. Adverse Drug Events

The most common adverse drug events reported with PCSK9 Inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with PCSK9 Inhibitors[2,3]

Adverse Events	Alirocumab	Evolocumab
Nasopharyngitis	11.3	10.5
Upper respiratory infection	-	9.3
Injection site reactions	7.2	5.7
Back pain	-	6.2
Influenza	5.7	7.5
Urinary tract infection	4.8	4.5
Diarrhea	4.7	3.0
Bronchitis	4.3	-
Myalgia	4.2	4.0
Headache	-	4.0
Dizziness	-	3.7
Muscle spasms	3.1	-
Sinusitis	3.0	4.2
Cough	2.5	4.5
Contusion	2.1	-
Musculoskeletal pain	2.1	3.3
Hypertension	-	3.2
Diarrhea	-	3.0
Gastroenteritis	-	3.0

- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for PCSK9 Inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for PCSK9 Inhibitors[2,3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alirocumab	Primary hyperlipidemia, HeFH, or prevention of cardiovascular events: Injection: initial, 75 mg SQ every two weeks; maintenance and maximum, 150 mg SQ every two weeks; or 300 mg SQ every four weeks divided into 2 two injections of 150 mg HeFH undergoing LDL apheresis or HoFH Injection: initial, maintenance, and maximum: 150 mg SQ once every 2 weeks	Safety and efficacy in children have not been established.	Single-dose prefilled pen or syringe: 75 mg 150 mg
Evolocumab	Primary hyperlipidemia, HeFH or prevention of cardiovascular events: Injection: initial, maintenance, and maximum: 140 mg SQ every 2 weeks, or 420 mg SQ once monthly in abdomen, thigh or upper arm HoFH:	HoFH in patients ≥10 years of age: Injection: initial, maintenance, and maximum: 140 mg SQ every 2 weeks or 420 mg SQ once monthly in abdomen, thigh or	Single-dose prefilled auto-injector, syringe, or on-body infusor: 140 mg 420 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: initial, maintenance, and maximum: 420 mg SQ once monthly	upper arm <u>HoFH in patients ≥10 years of age:</u> Injection: initial, maintenance, and maximum: 420 mg SQ once monthly	

HeFH=heterozygous familial hypercholesterolemia, HoFH=homozygous familial hypercholesterolemia, SQ=subcutaneous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of PCSK9 Inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with PCSK9 Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kereiakes et al.[15,16] (2015) ODYSSEY COMBO I Alirocumab 75 mg injected SC every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL) vs placebo Patients continued to take statin therapy with or without other lipid lowering therapy.	DB, MC, PG, RCT Patients ≥18 years of age with established heart disease or CHD equivalent, with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥100 mg/dL and no established heart disease but at a high risk for CVE and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening	N=316 52 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Percentage of patients achieving LDL-C <70 mg/dL, other lipid parameters and safety evaluations	Primary: Alirocumab was associated with a significantly greater reduction in LDL-C from baseline to week 24 compared with placebo (48.2% vs 2.3%; P<0.0001). At week 12, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose. In patients with a dose increase, LDL-C was reduced by an additional mean 22.8% at week 24 compared with week 12. These patients achieved similar reductions in LDL-C as those not requiring a dose increase (N=32). Secondary: LDL-C <70 mg/dL was achieved by 75% of the alirocumab group compared to 9% of the placebo group at week 24. Significant reductions from baseline to week 24 after therapy with alirocumab (P<0.0001 vs placebo) were observed in non–HDL-C (−39.1% vs −1.6%), apoB (−36.7% vs −0.9%), TC (−27.9% vs −2.9%), and lipoprotein(a) (−20.5% vs −5.9%). No significant change was observed in TG levels; whereas, a significant increase in HDL-C was observed in the alirocumab group (3.5% vs −3.8%; P<0.0001). The frequency of treatment-emergent adverse events and study medication discontinuations were generally comparable between treatment groups.
Cannon et al.[15,17] (2015) ODYSSEY COMBO II Alirocumab 75 mg injected SC every two weeks (dose increased to 150 mg at week 12 if LDL ≥1.8 mmol/L)	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age with established heart disease or CHD equivalent, LDL-C ≥70 mg/dL and	N=720 104 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Absolute	Primary: Alirocumab was associated with a significantly greater reduction in mean LDL-C from baseline at week 24 compared to ezetimibe (50.6 ± 1.4% vs 20.7 ± 1.9%; 29.8% ± 2.3% difference; P<0.0001). Secondary: Seventy seven percent of alirocumab and 45.6% of ezetimibe patients achieved LDL-C <1.8 mmol/L (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ezetimibe 10 mg QD Patients continued to take statin therapy. Other lipid lowering therapy was not permitted. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet for the duration of the study.	established heart disease or LDL-C ≥ 100 mg/dL and no established heart disease but at a high risk for CVE and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening		cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations and safety evaluations	As compared with the ezetimibe group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and had a modest increase in levels of HDL-C (P<0.0001 for all comparisons). TG were reduced from baseline to week 24 by 13.0 ± 1.5% in the alirocumab group and by 12.8 ± 2.0% in the ezetimibe group, but the difference between treatment arms was not statistically significant. Alirocumab was generally well tolerated, with no evidence of an excess of treatment-emergent adverse events. Adjudicated cardiovascular events were infrequent, occurring in 4.8% (n=23) of the alirocumab group vs 3.7% (n=9) in the ezetimibe group. Treatment-emergent local injection site reactions occurred in 2.5% of patients in the alirocumab arm vs 0.8% for ezetimibe arm.
Robinson et al.[18] (2015) ODYSSEY LONG TERM Alirocumab 150 mg injected SC every two weeks vs placebo Patients continued to take statin therapy with or without other lipid lowering agents. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet for the duration of the study.	DB, MC, PC, RCT Patients ≥18 years of age at a high risk for CVE (with HeFH or with established heart disease or CHD equivalent) with LDL ≥70 mg/dL receiving statins at maximum tolerated dosage for at least four weeks before screening	N=2,341 78 weeks	Primary: Percent change from baseline in LDL-C at week 24 Secondary: Absolute cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations, major cardiovascular events (death from CHD, nonfatal MI, fatal or nonfatal	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to placebo (−61.0% vs 0.08%; −62% placebo-corrected difference; P<0.0001). This effect remained consistent over 78 weeks. Secondary: The mean absolute LDL-C level at week 24 was 48 mg/dL in the alirocumab group and 119 mg/dL in the placebo group, corresponding to a mean absolute change from baseline of −74 mg/dL and −4 mg/dL, respectively (P<0.0001). The goal of an LDL-C level of <70 mg/dL at week 24 was met by 79.3% of the patients in the alirocumab group compared to 8.0% of the patients in the placebo group (P<0.001). As compared with the placebo group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and triglycerides and had a modest increase in levels of HDL-C and apolipoprotein A1 (P<0.001 for all comparisons). In a post hoc analysis, the rate of major adverse cardiovascular events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			ischemic stroke, or unstable angina requiring hospitalization), adherence rates and safety evaluations	was lower with alirocumab than with placebo (1.7% vs 3.3%; HR, 0.52; 95% CI, 0.31 to 0.90; P=0.02). Adherence was 98.0% and 97.6% in the alirocumab group and the placebo group, respectively. The alirocumab group, as compared with the placebo group, had higher rates of injection-site reactions (5.9% vs 4.2%), myalgia (5.4% vs 2.9%), neurocognitive events (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%).
Roth et al.[19] (2015) ODYSSEY MONO Alirocumab 75 mg injected SC every two weeks (dose increased to 150 mg at week 8 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD	DB, MC, PC, RCT Patients with primary hyper-cholesterolemia and moderate risk for CVE and LDL-C ≥100mg/dL and ≤190mg/dL	N=103 34 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to ezetimibe (47.2% vs 15.6%; P<0.0001). Secondary: Safety parameters and adverse events were similar between the two groups. The most common class of adverse events was infections (39.2% with ezetimibe vs 42.3% with alirocumab), which included nasopharyngitis, influenza, and upper respiratory tract infection. Injection-site reactions occurred in less than 2% of patients in both groups. Muscle-related adverse events occurred in 3.9% of patients treated with ezetimibe and 3.8% of patients treated with alirocumab.
Bays et al.[20,21] (2015) ODYSSEY OPTIONS I Alirocumab 75 mg injected SC every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD vs	AC, DB, MC, PG, RCT Patients ≥18 years of age with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥ 100 mg/dL and risk factors for CVE	N=355 24 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: Among atorvastatin 20 and 40 mg regimens respectively, there was a significantly greater decrease in LDL-C with alirocumab add-on from baseline at week 24 compared to add-on ezetimibe, double dose atorvastatin and switching to rosuvastatin (44.1% and 54.0% vs 20.5% and 22.6%, 5.0% and 4.8%, and 21.4%; P<0.001 vs all comparators). Most alirocumab-treated patients (86%) maintained their 75 mg every two weeks regimen. Secondary: Treatment-emergent adverse events occurred in 65.4% of alirocumab patients, compare to 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin (data pooled).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atorvastatin (at double baseline dose) vs rosuvastatin 40 mg QD (atorvastatin 40 mg baseline dose cohort only) Prior to randomization, patients were stabilized on atorvastatin 20 mg to 40 mg QD.				
Farnier et al.[22] (2016) ODYSSEY OPTIONS II Add-on alirocumab 75 mg every 2 weeks (1-mL subcutaneous injection via pre-filled pen) vs add-on ezetimibe 10 mg/day vs double-dose rosuvastatin All patients received baseline rosuvastatin regimens (10 or 20 mg)	DB, DD, MC, RCT Patients with cardiovascular disease and LDL–C ≥70 mg/dL or cardiovascular disease risk factors and LDL–C ≥100 mg/dL	N=305 24 weeks	Primary: Percent change in calculated LDL–C from baseline to 24 weeks Secondary: Percent change from baseline in calculated LDL–C on-treatment at Week 24 in the modified ITT (mITT) population (on-treatment analysis), percent change in LDL–C from baseline to Week 12 (ITT and on-treatment), the	Primary: In the baseline rosuvastatin 10 mg regimen ITT analysis, alirocumab add-on treatment significantly reduced LDL–C levels at Week 24 versus the other comparators (P<0.0001). From baseline, add-on alirocumab reduced LDL–C by 50.6%, add-on ezetimibe reduced LDL–C by 14.4%, and double-dose (20 mg) rosuvastatin reduced LDL–C by 16.3%. In the baseline rosuvastatin 20 mg regimen ITT analysis, mean reductions from baseline in LDL–C at Week 24 were greater in the alirocumab add-on group versus the other comparators. LDL–C reductions were 36.3% in the add-on alirocumab group, compared with 11.0% in the add-on ezetimibe group (P=0.0136) and with 15.9% in the double-dose (40 mg) rosuvastatin group (P=0.0453). However, the pre-specified threshold P-value for these 4-way comparisons was 0.0125; therefore, both primary comparisons failed to reach statistical significance in the baseline rosuvastatin 20 mg regimen. Secondary: As a result of both primary comparisons failing to reach statistical significance, all key secondary efficacy endpoints were not tested for statistical significance with respect to the two comparisons in the baseline rosuvastatin 20 mg regimen.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			percent change in other lipid parameters, and the proportion of very-high and high CV risk patients reaching LDL–C <70 mg/ or <100 mg/ at Week 24, respectively, in both ITT and on-treatment analyses; Safety	In the baseline rosuvastatin 10 mg regimen groups, the proportion of patients at very-high and high CV risk who reached a LDL–C level of <70 mg/dL or <100 mg/dL at Week 24, depending on risk status, was significantly greater in the alirocumab add-on group (84.9%) compared with the ezetimibe add-on group (57.2%; P=0.0007) and the rosuvastatin 20 mg group (45.0%; P<0.0001). The proportion of patients who reached the more stringent LDL–C level of <70 mg/dL at Week 24 was also significantly greater in the alirocumab add-on group (77.8%) compared with the ezetimibe add-on and rosuvastatin 20 mg groups (43.1%; P<0.0001 and 31.3%; P<0.0001), respectively. Treatment-emergent adverse events occurred in 56.3% of alirocumab patients versus 53.5% ezetimibe and 67.3% double-dose rosuvastatin (pooled data).
Moriarty et al.[23] (2015) ODYSSEY ALTERNATIVE Alirocumab 75 mg SC every 2 weeks vs ezetimibe 10 mg/ day vs atorvastatin 20 mg/ day	AC, DB, MC, PG, RCT Patients with primary hypercholesterolemia at moderate to high cardiovascular risk with statin intolerance (unable to tolerate ≥2 statins, including one at the lowest approved starting dose) due to muscle symptoms	N=314 24 weeks	Primary: Percent change in calculated LDL–C from baseline to 24 weeks Secondary: Change from baseline to 24 weeks using on-treatment (modified ITT) LDL-C values, and percent change from baseline to 12 and 24 weeks in LDL-C, apolipoprotein B, non–HDL-C, total cholesterol,	Primary: For the primary ITT efficacy analysis, LS mean change in LDL-C concentrations from baseline to week 24 were −45.0% for alirocumab and −14.6% for ezetimibe, with a difference between groups of −30.4% (P<0.0001). Secondary: For the on-treatment analysis, the change from baseline was −52.2% for alirocumab and −17.1% for ezetimibe (LS mean difference of −35.1%:,P<0.0001). A substantial reduction in LDL-C concentration occurred over the first four weeks, which was greater in the alirocumab arm and persisted throughout the 24-week treatment period. At week 24, 52 (41.9%) patients on alirocumab and 5 (4.4%) of those on ezetimibe (P<0.0001; ITT analysis) reached an LDL-C goal of <70 mg/dL in very high cardiovascular risk patients or <100 mg/dL in moderate-to-high-risk patients. Corresponding results in the on-treatment population were 51.2% and 5.6% (P<0.0001). The greater effect of alirocumab relative to ezetimibe on LDL-C-lowering from baseline to week 24 was consistent across most of the prespecified subgroups in the ITT population. In addition, reductions in apolipoprotein B, non–HDL-C, total cholesterol and lipoprotein(a) concentrations were greater for alirocumab vs ezetimibe (all P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			lipoprotein(a), HDL-C, apolipoprotein A1, and fasting triglyceride concentrations; adverse events	There were no statistically significant differences between the two groups in changes in triglyceride, HDL-C, and apolipoprotein A1 concentrations. Overall rates of treatment-emergent and serious AEs were generally similar between treatment arms, and there were no deaths in the study.
Schwartz et al.[24] (2018) ODYSSEY OUTCOMES Alirocumab 75 mg SC every 2 weeks vs placebo	DB, MC, PC, RCT Patients who had an acute coronary syndrome one to 12 months earlier, had LDL-C ≥70 mg/dL, non−HDL ≥100 mg/dL, or apoB ≥80 mg/dL, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose	N=18,924 Median follow-up of 2.8 years	Primary: Composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization Secondary: Any coronary heart disease even; major coronary heart disease event; any cardiovascular event; death	Primary: A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group; The Kaplan–Meier probability estimate at four years was 12.5% in the alirocumab group and 14.5% in the placebo group (HR, 0.85; 95% CI, 0.78 to 0.93; P<0.001). Secondary: Among the main secondary end points, the risks of any coronary heart disease event, major coronary heart disease events, any cardiovascular event, and a composite of death from any cause, nonfatal MI, or nonfatal ischemic stroke were lower among patients treated with alirocumab than among those who received placebo. A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (HR, 0.85; 95% CI, 0.73 to 0.98).
Ray et al.[25] (2018) ODYSSEY DM-DYSLIPIDEMIA Alirocumab 75 mg SC every 2 weeks (may increase to 150 mg at week 12)	MC, OL, RCT Patients ≥18 years of age with type 2 diabetes and mixed dyslipidemia not optimally managed by maximally tolerated statins	N=413 24 weeks	Primary: Percentage change in non-HDL cholesterol from baseline to week 24 Secondary: Safety	Primary: The least-squares mean percentage change from baseline to week 24 in non-HDL cholesterol was −37.3 (3.0%) with alirocumab and −4.7 (3.3%) with usual care (−32.5% difference vs usual care; 97.5% CI, −38.1 to −27.0; P<0.0001). Alirocumab also lowered levels of measured LD-C, ApoB, total cholesterol and Lp(a) vs usual care (all P<0.0001). Secondary: The percentage of individuals who experienced any treatment-emergent

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs usual care (no additional lipid-lowering therapy; fenofibrate; ezetimibe; omega-3 fatty acid; nicotinic acid)				adverse events, treatment-emergent serious adverse events and treatment-emergent adverse events leading to discontinuation was similar in the alirocumab and usual care groups. The treatment-emergent adverse events occurring in ≥2% of individuals were reported at generally similar frequencies in the alirocumab and usual care groups, with some treatment-emergent adverse events occurring at higher frequency in the alirocumab vs usual care group and vice versa; urinary tract infection (alirocumab: 5.8%; usual care: 3.6%) and diarrhea (alirocumab: 5.1%; usual care: 6.6%) were the most common treatment-emergent adverse events.
Blom et al.[26] (2020) ODYSSEY HoFH Alirocumab 150 mg SC every 2 weeks vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with a clinical or genetic diagnosis of HoFH and LDL-C ≥70 mg/dL and receiving a statin or documented statin intolerance	N=69 32 weeks	Primary: Percent change in LDL-C from baseline to week 12 Secondary: Percent change from baseline to week 12 in apoB, non-HDL-C, TC, HDL-C, TG, apolipoprotein A1, lipoprotein(a) and safety evaluations	Primary: At week 12, the least-squares mean (±SE) reduction in LDL-C from baseline was −26.9 ± 4.6% with alirocumab and 8.6 ± 6.3% with placebo (−35.6% ± 7.8% difference vs placebo; P<0.0001). Secondary: Alirocumab treatment, as compared with placebo, resulted in significant least-squares mean percent reductions from baseline in levels of apoB, non-HDL-C, TG, and lipoprotein(a); P<0.0001 for each endpoint. Evolocumab treatment resulted in a least-squares mean difference of 3.6 ± 3.8% in the HDL-C (P=0.3541), -11.3 ± 7.1 in TG (P=0.1112), and 3.6 ± 3.6% in the apolipoprotein A1 (P=0.3212) compared to placebo. The most common adverse events were upper respiratory tract infection, headache, and diarrhea.
Jukema et al.[27] (2019) Stroke in ODYSSEY OUTCOMES Alirocumab 75 mg SC every 2 weeks	DB, PB, MC, RCT Patients ≥40 years of age who had been hospitalized with myocardial infarction or unstable angina	N=18,924 Median follow-up 2.8 years	Primary: Risk of nonfatal or fatal ischemic or hemorrhagic stroke Secondary: Multivariable	Primary: Alirocumab reduced the risk of any stroke HR, 0.72 (95% CI, 0.57 to 0.91; P=0.005) and ischemic stroke HR, 0.73 (95% CI, 0.57 to 0.93; P=0.01) without increasing hemorrhagic stroke HR, 0.83 (95% CI, 0.42 to 1.65; P=0.59). Secondary: History of cerebrovascular disease was the strongest predictor of any

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	and LDL ≥70 mg/dL		predictors of any stroke	stroke HR, 2.469 (95% CI, 1.792 to 3.401; P<0.0001). Glomerular filtration rate <60 mL/min/1.73 m^2, diabetes, heart failure, myocardial infarction, oral anticoagulants, current smoking and peripheral artery disease, increasing age, systolic blood pressure, and LDL-C were associated with an increased risk of all-cause stroke (P<0.05).
Trankle et al.[28] (2019) VCU-AlirocRT Alirocumab 150 mg SC vs placebo	DB, PC, RCT Patients ≥18 years of age on a high-intensity statin, with LDL-C >70 mg/dL and admitted to hospital with non-ST elevation myocardial infarction	N=20 14 days	Primary: Placebo-corrected change in LDL-C at 14 days Secondary: Placebo-corrected change in high-sensitivity C-reactive protein, tumor necrosis factor-α, interleukin-6 and 10, free PCSK9, total PCSK9 levels at 72 hours and 14 days, change in LDL-C at 72 hours and safety	Primary: Patients treated with alirocumab had a reduction in LDL-C levels from 91 mg/dL, to 73 mg/dL, and 28 mg/dL at baseline, 72 hours, and 14 days, respectively; P<0.01). Secondary: There were no significant changes in free or total PCSK9 levels in the placebo group; P>0.2. Free PCSK9 levels were reduced to undetectable levels in patients treated with alirocumab at 72 hours and 14 days. Total PCSK9 levels increased at each time point in the alirocumab group. High-sensitivity C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-10 levels did not change significantly from baseline in either group. No adverse events that occurred were attributed to the medication.
Blom et al.[29] (2014) DESCARTES Evolocumab 420 mg injected SC once monthly vs	DB, MC, PC, RCT Patients 18 to 75 years of age with an LDL-C ≥75 mg/dL and TG ≤400 mg/dL	N=901 52 weeks	Primary: LDL-C at 52 weeks Secondary: LDL-C at week 12 and percentage of	Primary: At 52 weeks, the least-squares mean (±SE) reduction in LDL-C from baseline in the evolocumab group, taking into account the change in the placebo group, was 57.0 ± 2.1% at week 52. In the analysis according to background-therapy group, the least-squares mean reduction in LDL-C in the evolocumab group, taking into account the change in the placebo group, was 55.7 ± 4.2% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Patients received 1) diet alone, 2) diet with atorvastatin 10 mg QD, 3) diet with atorvastatin 80 mg QD, 4) or diet with atorvastatin 80 mg QD plus 10 mg of ezetimibe QD An initial four week run-in patients with CHD or risk equivalent and LDL-C ≥100 mg/dL or without CHD or risk equivalent and LDL-C ≥130 mg/dL were randomized to background treatment noted above. Treatment was continued in four-week increments with increases in background intensity for patients not at CHD-based goal noted above. Patients were randomized to treatment once at or below CHD-based goal.			patients with LDL-C <70 mg/dL at week 52, TC, HDL-C, non-HDL-C, VLDL, apoB, apoB/ apolipoprotein A1, lipoprotein (a), TG and safety evaluations	the diet-alone group, 61.6 ± 2.6% in the group receiving 10 mg of atorvastatin, 56.8 ± 5.3% in the group receiving 80 mg of atorvastatin and 48.5 ± 5.2% in the group receiving 80 mg of atorvastatin plus 10 mg of ezetimibe (P<0.001 for all comparisons). Secondary: The least-squares mean (±SE) reduction in LDL-C from baseline in the evolocumab group, taking into account the change in the placebo group, was 57.5 ± 1.6% at week 12. The level of LDL-C was reduced below 70 mg/dL in 82.3% of patients in the evolocumab group, as compared with 6.4% of those in the placebo group. Evolocumab treatment, as compared with placebo, also resulted in significant least-squares mean percent reductions from baseline in levels of apoB, non-HDL-C, lipoprotein(a) and TG (P values not reported). Evolocumab treatment resulted in a least-squares mean increase of 5.4 ± 1.1% in the HDL-C (P<0.001) and of 3.0 ± 0.8% in the apolipoprotein A1 (P<0.001). The most common adverse events were nasopharyngitis, upper respiratory tract infection, influenza and back pain.
Stroes et al.[30] (2014) GAUSS-2 Evolocumab 140 mg injected SC every two weeks vs	AC, DB, MC, RCT Patients 18 to 80 years of age with an LDL-C above ATP III goal and a previous intolerance to ≥2 statins	N=307	Primary: LDL-C at week 12 and mean of weeks 10 and 12 Secondary: Percentage of patients with LDL-C <70	Primary: Evolocumab reduced LDL-C from baseline by 53% (every two weeks) to 56% (monthly), corresponding to treatment differences versus ezetimibe of 37 to 39% (P<0.001). Mean percent reductions from baseline and treatment differences at week 12 were similar (P<0.001). Secondary: Evolocumab-treated patients were more likely to achieve LDL-C target levels than ezetimibe-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
evolocumab 420 mg injected SQ monthly vs ezetimibe 10 mg QD			mg/dL, non HDL-C, apoB, apoB/apolipoprotein A1, lipoprotein (a), TG, TC/HDL-C, VLDL and safety evaluations.	Compared with ezetimibe, evolocumab led to significant reductions in apoB, lipoprotein(a), non–HDL-C and the apoB/apolipoprotein A-I and TC/HDL-C ratios (P<0.001) Muscle adverse events occurred in 12% of evolocumab-treated patients and 23% of ezetimibe-treated patients. Treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups.
Nissen et al.[31] (2016) GAUSS-3 Evolocumab (420 mg monthly subcutaneously) vs ezetimibe (10 mg daily by mouth)	DB, DD, RCT Patients 18 to 80 years of age with elevated LDL-C levels who were unable to tolerate an effective dose of a statin because of muscle-related adverse effects	N=491 24-week crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin but not placebo; followed by 2-week washout; followed by 24-week comparison	Primary: Mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels Secondary: Absolute change from baseline in LDL-C level; percent change from baseline in levels of total cholesterol, non–high-density lipoprotein cholesterol (non–HDL-C), and apolipoprotein B (ApoB); percent change from baseline in total	Primary: Mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels showed a least-squares mean change of −16.7% (95% CI, −20.5 to −12.9%) for ezetimibe and −54.5% (95% CI, −57.2 to −51.8%) for evolocumab: a mean difference of −37.8% (95% CI, −42.3 to −33.3%; P<0.001). Mean percent change in LDL-C level from baseline to the week 24 showed a least-squares mean change of −16.7% (95% CI, −20.8 to −12.5%) for ezetimibe and −52.8% (95% CI, −55.8 to −49.8%) for evolocumab: a mean difference of −36.1% (95% CI, −41.1 to −31.1%; P<0.001). Secondary: Secondary end points including percent changes in levels of total cholesterol, non–HDL-C, and ApoB; total cholesterol to HDL-C ratio; and ApoB to apolipoprotein A1 ratio showed similar results, with P<0.001 demonstrating greater cholesterol reductions in the evolocumab group. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (P=0.17). Active study drug was stopped for muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cholesterol to HDL-C ratio and ApoB to apoliprotein A1 ratio; and the percentage of patients achieving an LDL-C level less than 70 mg/dL; safety	
Robinson et al.[32] (2014) LAPLACE-2 Evolocumab 140 mg injected SQ every two weeks vs evolocumab 420 mg injected SQ once monthly ezetimibe 10 mg QD (atorvastatin group only) vs placebo During a four-week run in period, patients were initially randomized to a moderate-intensity (atorvastatin 10 mg QD, simvastatin 40 mg QD or	AC, DB, MC, PC, RCT Patients 18 to 80 years of age with LDL-C ≥150 mg/dL (not on statin), ≥100 mg/dL (non-intensive statin) or ≥80 mg/dL (intensive statin [defined as daily atorvastatin (40mg or greater), rosuvastatin (20mg or greater), simvastatin (80 mg), or any statin plus ezetimibe]) and TG<400 mg/dL	N=2,067 12 weeks	Primary: LDL-C at week 12 and mean of weeks 10 and 12 Secondary: Mean at weeks 10 and 12 and at week 12 for the change from baseline in LDL-C level, the percent change from baseline in additional lipid parameters, the proportion of patients achieving LDL-C levels less than 70mg/dL, and safety evaluations.	Primary: Evolocumab reduced LDL-C levels by 66% (95% CI, 58 to 73%) to 75% (95% CI, 65 to 84%) (every two weeks) and by 63% (95% CI, 54 to 71%) to 75% (95% CI, 67 to 83%) (monthly) compared to placebo at the mean of weeks 10 and 12 in the moderate- and high-intensity statin-treated groups. Secondary: For moderate-intensity statin groups, evolocumab every two weeks reduced LDL-C from a baseline mean of 115 to 124 mg/dL to 39 to 49 mg/dL; monthly evolocumab reduced LDL-C from a baseline mean of 123 to 126 mg/dL to 43 to 48 mg/dL. For high-intensity statin groups, evolocumab every two weeks reduced LDL-C from a baseline mean of 89 to 94 mg/dL to 35 to 38 mg/dL; monthly evolocumab reduced LDL-C from a baseline mean of 89 to 94 mg/dL to 33 to 35 mg/dL. Evolocumab administered every two weeks and monthly resulted in significant reductions in non-HDL-C, apoB and lipoprotein(a) for all statin groups. Ninety four percent and 93 to 95% of patients receiving evolocumab every two weeks and monthly reached an LDL-C of <70 mg/dL, respectively. The most common adverse events in evolocumab-treated patients were back pain, arthralgia, headache, muscle spasms and pain in extremity

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosuvastatin 5 mg QD) or high-intensity (atorvastatin 80 mg QD or rosuvastatin 40 mg QD) statin.				(all <2%).
Koren et al.[33] (2014) MENDEL-2 Evolocumab 140 mg injected SC every two weeks vs evolocumab 420 mg injected SC once monthly vs ezetimibe 10 mg QD vs placebo	AC, DB, MC, PC, RCT Patients 18 to 80 years of age with LDL-C≥ 100 mg/dL, <190 mg/dL and Framingham risk scores ≤10%	N=614 12 weeks	Primary: LDL-C at week 12 and mean of weeks 10 and 12 Secondary: Proportion of patients achieving LDL-C <70 mg/dL, other lipid parameters and safety endpoints	Primary: Evolocumab treatment reduced LDL-C from baseline, on average, by 55 to 57% more than placebo and 38 to 40% more than ezetimibe (P<0.001 for all comparisons). At 12 weeks, LDL-C levels had decreased from baseline, on average, by 57.0% (95% CI, 59.5 to 54.6%) with biweekly evolocumab compared with 0.1% (95% CI, 3.2 to 3.4%) for placebo and 17.8% (95% CI, 21.0 to 14.5%) for ezetimibe (P<0.001). For patients administered monthly evolocumab, the mean 12-week LDL-C reduction was 56.1% (95% CI, 58.3% to 53.9%) compared to 1.3% (95% CI, 4.4%to 1.7%) for placebo and 18.6% (95%CI, 21.6% to 15.5%) for ezetimibe (P<0.001). LDL-C percent changes from baseline for the mean of weeks 10 and 12 and the absolute mean reductions in LDL-C levels were significant in all evolocumab groups compared with placebo and ezetimibe (P<0.001). Secondary: Patients in the evolocumab groups achieved a level of LDL-C <70 mg/dl at much higher rates (72% and 69%) than placebo (0% and 1%) or ezetimibe (2% and 1%) group patients for the mean of weeks 10 and 12 and at week 12, respectively. Evolocumab significantly decreased levels of apoB, lipoprotein (a), and non–HDL-C, TC/HDL-C and apoB/apolipoprotein A1. Significant HDL-C increases were observed with evolocumab (P<0.05). TG and VLDL were significantly lowered with monthly evolocumab vs placebo or ezetimibe and in some comparisons in the biweekly group. Evolocumab treatment also favorably altered other lipoprotein levels.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Treatment-emergent adverse events, muscle-related adverse events and laboratory abnormalities were comparable across treatment groups.
Sabantine et al.[34] (2015) OSLER-1/2 Evolocumab 140 mg injected SC every two weeks (OSLER-2) or 420 mg once monthly (OSLER 1 or 2 [based upon patient preference]) vs standard therapy alone Evolocumab was administered in combination with other standard therapies based upon local guidelines for cholesterol treatment.	ES, MC, OL, RCT (extension study of five phase II trials (OSLER-1) or seven phase III trials (OSLER-2) Patients with hyperlipidemia (trials included patients on monotherapy, combination with statin with or without ezetimibe, statin intolerant patients, patients with HeFH)	N=4,465 56 weeks randomized followed by ongoing non-randomized open-label evaluation (OSLER-1) 48 weeks by ongoing non-randomized open-label evaluation (OSLER-2)	Primary: Safety endpoints Secondary: LDL-C, non–HDL-C, HDL-C, TC, TG, apolipoprotein A1 and apoB, lipoprotein(a). and CVE	Primary: Most adverse events occurred with similar frequency in the two groups, although neurocognitive events were reported more frequently in the evolocumab group. The risk of adverse events, including neurocognitive events, did not vary significantly according to the achieved level of LDL-C. Secondary: As compared with standard therapy alone, evolocumab reduced the level of LDL-C by 61%, from a median of 120 mg/dL to 48 mg/dL at 12 weeks (P<0.001). At 12 weeks, the LDL-C was reduced to ≤100 mg/dL in 90.2% of patients and to ≤70 mg/dL in 73.6% of patients in the evolocumab group, as compared with 26.0% and 3.8%, respectively, in the standard-therapy group. In the evolocumab group, as compared with the standard-therapy group, changes in related atherogenic lipid measures were similar to those observed for LDL-C, with reductions of 52.0% in non-HDL-C, 47.3% in apoB, 36.1% in TC, 12.6% in TG, and 25.5% in lipoprotein(a) (P<0.001 for all comparisons) Evolocumab also raised levels of HDL-C and apolipoprotein A1 by 7.0% and 4.2%, respectively (P<0.001 for both comparisons). The rate of CVE at one year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (HR in the evolocumab group, 0.47; 95% CI, 0.28 to 0.78; P=0.003).
Raal et al.[35] (2015) RUTHERFORD-2 Evolocumab 140 mg injected SC every two weeks	DB, PC, MC, RCT Patients 18 to 80 years age who met clinical criteria for HeFH and were on stable lipid-	N=331 12 weeks	Primary: LDL-C at week 12 and mean of weeks 10 and 12 Secondary:	Primary: Compared with placebo, evolocumab at both dosing schedules led to a significant reduction in mean LDL-C at week 12 (biweekly dose: 59.2% reduction [95% CI, 53.4% to 65.1%], monthly dose: 61.3% reduction [53.6% to 69.0%]; both P<0.0001) and at the mean of weeks 10 and 12 (60.2% reduction [95% CI, 54.5% to 65.8%] and 65.6% reduction [59.8% to 71.3%]; both P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs evolocumab 420 mg injected SC once monthly vs placebo	lowering therapy for at least four weeks, with LDL-C≥ 100 mg/dL		Other lipid parameters and safety endpoints	Secondary: Mean reductions in lipoprotein(a) and apoB at week 12 were significantly greater in both evolocumab groups than in the placebo groups (P<0.05 for all comparisons). At week 12, evolocumab 140 mg every two weeks reduced TG concentrations compared with placebo, whereas the 420 mg monthly evolocumab dose resulted in a smaller, but still significant, decrease compared with placebo (P<0.05 for all comparisons). Both doses of evolocumab led to significant increases in HDL-C compared with placebo (P<0.05 for all comparisons). The most common adverse events occurring more frequently in the evolocumab-treated patients than in the placebo groups were nasopharyngitis (19 patients [9%] vs five [5%], respectively) and muscle-related adverse events (ten patients [5%] vs one [1%], respectively).
Raal et al.[36] (2015) TESLA-B Evolocumab 420 mg injected SC once monthly vs placebo Evolocumab was administered in combination with other standard therapies based upon local guidelines for cholesterol treatment.	DB, MC, PC, RCT Patients aged ≥12 years with HoFH diagnosed either by genetic analysis or clinical criteria and LDL-C >3.4 mmol/L (61.2 mg/dL) after at least four weeks of a stable, low-fat diet and baseline lipid-lowering therapies, fasting TG <81 mg/dL and body weight ≥40 kg	N=50 12 weeks	Primary: LDL-C at week 12 Secondary: Other lipid parameters and safety endpoints	Primary: Compared with placebo, evolocumab significantly reduced LDL-C at 12 weeks by 30.9% (95% CI, –43.9% to –18.0%; P<0.0001). The least-squares mean absolute reduction in LDL-C with evolocumab versus placebo at week 12 was 2.4 mmol/L (43.2 mg/dL; 95% CI, –3.7 to –1.1). Secondary: Evolocumab treatment led to a significant least-squares mean reduction in apoB at week 12 compared to placebo (P=0.0002). No differences between the two treatment groups were recorded in HDL-C or TG at week 12 (P values not reported). Treatment-emergent adverse events occurred in ten (63%) of 16 patients in the placebo group and 12 (36%) of 33 in the evolocumab group. No serious clinical or laboratory adverse events occurred, and no anti-evolocumab antibody development was detected during the study.
Sabatine et al.[37]	DB, PC, RCT	N=27,564	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2017) FOURIER Evolocumab 140 mg injected SC every two weeks vs Evolocumab 240 mg injected SC once monthly vs placebo	Patients (40 to 85 years of age) with LDL-C≥70 mg/dL or non-HDL 100mg/dl or higher and a history of MI, ischemic stroke, or symptomatic PAD who were on optimized statin therapy (atorvastatin 20 mg QD or equivalent statin) with or without ezetimibe	26 months	Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina or coronary revascularization Secondary: Composite of cardiovascular death, MI or stroke, other lipid parameters	Compared to placebo, evolocumab significantly reduced the risk of the primary endpoint by 1.5% (11.3% vs 9.8%; HR, 0.85; 95% CI, 0.79 to 0.92; P<0.001). Secondary: Compared to placebo, evolocumab significantly reduced the risk of the secondary endpoint by 1.5% (7.4% vs 5.9%; HR, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL-C levels (median, 74 mg/dL). Although the aggregated results demonstrated a benefit in the primary and key secondary endpoint, individual components of the composite endpoint may not have shown a difference. For example, there was no difference in death from any cause in the evolocumab group compared to placebo (3.2% vs 3.1%; HR, 1.04; 95% CI, 0.91 to 1.19; P=0.54). There were no new significant safety concerns compared to earlier trials. There was a higher rate of injection site reactions in the evolocumab arm.
Santos et al.[38] (2020) HAUSER-RCT Evolocumab 420 mg SC once monthly vs placebo	DB, MC, PC, RCT Patients 10 to 17 years of age with HeFH with LDL ≥130 mg/dL and TG ≤400 mg/dL on a low-fat diet and stable lipid-lowering therapy	N=157 24 weeks	Primary: Percent change in LDL-C from baseline to week 24 Secondary: Mean percent change in LDL-C from baseline to weeks 22 and 24, absolute change in LDL-C at week 24, percent change in non-HDL-C,	Primary: At week 24 the difference in percent change in LDL-C in the evolocumab group compared to the placebo group was -38.3% (95% CI, -45.5 to -31.1; P<0.001). Secondary: The difference in mean absolute change in LDL-C from baseline to week 24 for evolocumab compared to placebo was -68.6 mg/dL (95% CI, -83.1 to -54.0; P<0.001). At weeks 22 and 24 the mean percent change from baseline in LDL-C was 48.0% vs -5.9% for evolocumab and placebo, respectively; P<0.001. The difference between evolocumab and placebo for percent change in non-HDL, apoB, ratio of TC to HDL-C, and ratio of apoB to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			apoB at week 24, ratio of TC to HDL-C, and apoB to apolipoprotein A1 at week 24	apolipoprotein A1 from baseline to week 24 were all statistically significant; P<0.001.
Santos et al.[39] (2022) HAUSER-OLE Evolocumab 420 mg SC once monthly	OL, single-arm Patients 10 to 17 years of age with HeFH who completed 24 weeks of monthly treatment with evolocumab 420 mg SC once monthly in HAUSER-RCT with no serious treatment emergent adverse events	N=150 80 weeks	Primary: Treatment emergent adverse events Secondary: Percentage changes and absolute changes from baseline in concentrations of LDL cholesterol, other lipid parameters, and PCSK9, changes from baseline in steroid hormones, liposoluble vitamins, fasting blood glucose, and HbA1c, changes in growth parameters, shift from baseline in Tanner developmental stages, abnormal muscle and liver enzyme	Primary: At least one treatment-emergent adverse event occurred in 105 (70%) of 150 patients: 36 (74%) of 49 patients in the placebo-evolocumab group and 69 (68%) of 101 in the evolocumab-evolocumab group. Most treatment-emergent adverse events were of Common Terminology Criteria for Adverse Events grade 1 or 2 severity. The events occurring in 5% or more patients overall were nasopharyngitis, headache, influenza-like illness, gastroenteritis, upper respiratory tract infection, oropharyngeal infection, oropharyngeal pain and fatigue. Secondary: After 80 weeks of open-label treatment with evolocumab, the mean percentage change from baseline of LDL cholesterol was -35.3% (SD=28.0). Other lipid parameters also showed sustained improvements throughout the open-label treatment period, and patterns were similar across the groups that received evolocumab versus those that received placebo in HAUSER-RCT. PCSK9 concentrations were reduced by a mean of 40.0% (SD=46.7), from a median of 3.7 nmol/L (IQR 3.0 to 4.7) at baseline to a median of 1.9 nmol/L (0.8 to 3.3) at the end of HAUSER-OLE. Evolocumab also had no adverse effect on steroid hormones, fat-soluble vitamins, fasting blood glucose or HbA1c. Growth variables and Tanner stages of pubertal development were numerically similar by treatment patients had received in the randomized controlled trial, and there was no indication of an effect of evolocumab on these variables. No clinically important abnormalities in muscle or liver enzymes were observed. During the neurological examination at week 80, all findings were normal, although two patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			concentrations, abnormal neurological findings at week 80, and changes in ECG parameters and vital signs	had an abnormal reflex finding. No clinically important abnormalities or changes from baseline were reported in ECG parameters at week 80.
Koren et al.[40] (2019) Evolocumab 420 mg SC once monthly vs standard of care	MC, OL, RCT Patients with hyperlipidemia that did not discontinue treatment due to a serious adverse event from previous qualifying phase 2 study participation	N=1,151 5 years	Primary: Safety and tolerability of long-term exposure by incidence of adverse events, serious adverse events, and discontinuation Secondary: Incidence of anti-drug antibodies	Primary: Over the five years 1,179 (94%) patients reported ≥1 adverse event, 293 (23%) reported a serious adverse event, and 71 (6%) patients discontinued evolocumab. Adverse event rates in year 5 (65%) were similar to the standard of care group in year one (74%). Common adverse events include nasopharyngitis, arthralgia, and upper respiratory tract infection with rates staying similar for each year. Secondary: Four patients tested positive for binding anti-drug antibodies, but none experienced a loss in treatment efficacy.
Kosinkas et al.[41] (2019) EVOPACS Evolocumab 420 mg SC once monthly vs placebo	DB, PC, RCT Patients ≥18 years of age hospitalized with acute coronary syndrome with symptom onset <72 hours or ST-segment elevation myocardial infarction and LDL-C ≥70 mg/dL	N=308 8 weeks	Primary: Percent change in LDL-C from baseline to week 8 Secondary endpoints: TC, non-HDL-C, TG, HDL-C, apoB, lipoprotein(a), safety	Primary: Percent change in LDL-C from baseline to week eight was -77.1 ± 15.8% in the evolocumab group versus -35.4 ± 26.6% in the placebo group, a difference of -40.7% (95% CI, -45.2% to -36.2%; P<0.001). Secondary: Evolocumab compared with placebo had reductions of 26.5% TC, 34.2% apoB, 34.6% non-HDL-C; P<0.001 and 20% TG; P=0.024. Evolocumab raised HDL-C by 4.8%; P=0.03. Most common adverse events reported include musculoskeletal pain, diarrhea, local injection site reaction, and nasopharyngitis.
Santos et al.[42]	OL, single arm	N=300	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2020) Evolocumab 420 mg SC once monthly Patients on lipoprotein apheresis received evolocumab 420 mg SC every 2 weeks	Patients with HoFH or HeFH ≥12 years of age on stable lipid-lowering therapy	5 years	Incidence of treatment-emergent adverse events Secondary: Lipid-lowering efficacy	The incidence of treatment-emergent adverse events were similar for both groups (HoFH and HeFH). The most common adverse events (≥10%) were nasopharyngitis, upper respiratory tract infection, headache, myalgia, and diarrhea. There were 11 patients that discontinued treatment due to adverse events. The mean percentage change in LDL-C at week 216 in patients with HoFH was -24.0 ± 41.3%. The mean percentage change in LDL-C at week 216 in patients with HeFH was -47.2 ± 27.9%. No p-values reported.

Drug regimen abbreviations: QD=once daily, SC=subcutaneously
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, ES=extension study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
apoB=apolipoprotein B, ATP=Adult Treatment Program, CHD=coronary heart disease, CI=confidence interval, CVE=cardiovascular events, CRP= C-reactive protein, ECT=electrocardiogram, HDL-C=high density lipoprotein, HeFH=heterozygous familial hypercholesterolemia, HoFH, homozygous familial hypercholesterolemia, HR=hazard ratio, IQR=interquartile range, LDL-C=low density lipoprotein cholesterol, SD=standard deviation, SE=standard error, TC=total cholesterol, TG=triglyceride, VLDL=very low density lipoprotein

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 PCSK9 Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alirocumab	injection	Praluent®	$$$$$	N/A
Evolocumab	injection	Repatha®	$$$$$	N/A

N/A=Not available

X. Conclusions

There are currently two Food and Drug Administration (FDA)-approved PCSK9 inhibitors commercially available. These agents include Praluent® (alirocumab) and Repatha® (evolocumab).[1] Both Praluent® (alirocumab) and Repatha® (evolocumab) are FDA-approved as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous and homozygous familial hypercholesterolemia) to reduce LDL-C.[2,3] Praluent® (alirocumab) is also indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. Repatha® (evolocumab) is also indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease and as an adjunct to diet and other lipid lowering therapies (statins, ezetimibe, LDL-C apheresis) in pediatric patients ≥10 years of age with homozygous familial hypercholesterolemia (HoFH) or heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C.[3]

The American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol was released in 2018. In patients with clinical atherosclerotic cardiovascular disease (ASCVD) who are judged to be very high risk, maximally tolerated LDL-C lowering therapy including maximally tolerated statin therapy and ezetimibe should be utilized before considering PCSK9 inhibitor therapy. It is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost in this patient population when LDL-C is >70 mg/dL despite maximally tolerated LDL-C lowering therapy. Patient preference should be considered in the discussion to initiate PCSK9 inhibitor therapy, including considerations of the patient's perception of net benefit, convenience/burden of additional therapy, cost, quality of life, and the potential to jeopardize adherence to other evidence-based therapies.[5] The 2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis recommend PCSK9 inhibitors be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH and individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.[6]

The FDA-approval of alirocumab is based on data from twelve phase III ODYSSEY trials (N>5,000) including patients with HeFH and HoFH, those with coronary heart disease (CHD) and those at risk for cardiovascular events (CVE).[2,15-20] Across the clinical trial program, alirocumab was associated with an approximate 40 to 60% decrease in LDL-C from baseline. In addition, other lipid measures generally decreased at higher levels than with placebo. The FDA-approval of evolocumab is based on data from ten phase III PROFICO trials (N~6,800). These trials included patients with elevated cholesterol on statins with or without other lipid-lowering therapies, patients who cannot tolerate statins, patients with HeFH, and patients with HoFH.[3,29-42] Across these clinical trials, evolocumab was evaluated at two dosing schedules, 120 mg every two weeks and 420 mg monthly. The agent was generally associated with a 40 to 60% reduction in LDL-C from baseline and a significant decrease in other lipid parameters compared to placebo. In addition, in an extension study of a phase II and III clinical trial (OSLER 1 and 2), the rate of cardiovascular events at one year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (HR, 0.47; 95% CI, 0.28 to 0.78; P=0.003).[34]

The FOURIER trial (N=27,564) was a double-blind, randomized, placebo-controlled trial which compared evolocumab to placebo in patients with a history of myocardial infarction (MI), ischemic stroke, or symptomatic peripheral artery disease (PAD) who had an LDL of 70 mg/dL or higher, or a non-HDL of 100 mg/dL or higher despite optimized statin therapy defined as atorvastatin 20 mg or equivalent.[37] The trial was associated with an absolute reduction of approximately 2% in the risk of the primary cardiovascular composite endpoint (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) after a median follow-up of 26 months. Key secondary endpoints, including a more significant composite cardiovascular endpoint (e.g., removes less severe cardiac outcomes including elective revascularization) and lipid measures also supported efficacy.[37] The ODYSSEY OUTCOMES trial (N=18,924) found that in patients who had an acute coronary syndrome one to 12 months earlier, had LDL-C ≥70 mg/dL, non−HDL ≥100 mg/dL, or apoB ≥80 mg/dL, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose, after a median follow-up of 2.8 years a composite coronary end-point event occurred in 9.5% of patients in the alirocumab group and in 11.1% of patients in the placebo group (HR, 0.85; 95% CI, 0.78 to 0.93; P<0.001).[27]

At this time, there is insufficient data to conclude that one PCSK9 inhibitor is safer or more efficacious than other brand or generic products within its class and that it offers a significant clinical advantage over other alternatives in general use. The drugs in this AHFS class are used in a specific patient population. Because these agents have narrow indications with limited usage, and very specific criteria must be met prior to initiating therapy, these agents should be made available 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 PCSK9 inhibitor 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antilipemic Agents, Miscellaneous
AHFS Class 240692
February 7, 2024

I. Overview

The antilipemic agents are categorized into six different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, HMG-CoA reductase inhibitors (statins), and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration (FDA)-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Niacin favorably affects all lipids and lipoproteins when given in pharmacological doses; however, the mechanism of action is not completely understood.[1-4] Niacin has several effects on lipid metabolism including inhibition of hepatic production of very low-density lipoprotein cholesterol (VLDL-C), and consequently its metabolite low-density lipoprotein cholesterol (LDL-C). In addition, it decreases plasma concentrations of triglycerides (TGs) (20 to 50%), very low-density lipoprotein remnants, and intermediate density lipoprotein. Administration of niacin also causes a shift in low-density lipoprotein composition from small, dense particles to larger, more buoyant particles. Lastly, niacin increases high density lipoprotein cholesterol (HDL-C) (15 to 35%) both by reducing lipid transfer of cholesterol from HDL-C to VLDL-C, and by delaying HDL-C clearance. Niacin can decrease LDL-C by 5 to 25%.[1-3]

Modifications in lipids can also be affected by a number of dietary approaches or specific dietary supplements. Like medication classes, these modalities also differ with respect to their mechanism of action and to the degree and type of lipid modification.[1] Rich sources of omega-3-fatty acids include fatty fish, certain vegetables and nuts, and fish oil as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). When administered at high doses they can reduce levels of TGs by approximately 50%.[1] The mechanism by which this occurs is thought to be caused by the inhibition of VLDL-C.[5,6] In general, omega-3-fatty acids have no effect on LDL-C, but large doses have been shown to reciprocally increase LDL-C levels in patients with hypertriglyceridemia.[1] Each omega-3 acid ethyl esters capsule (Lovaza®) contains at least 900 mg of ethyl esters of omega-3 fatty acids sourced from fish oil, which are predominantly EPA (approximately 465 mg) and DHA (approximately 375 mg).[5] The total EPA and DHA dose recommended for TG-lowering is approximately 2 to 4 g per day.[1,2] Vascepa® is an omega-3 fatty acid formulation. It also contains EPA obtained from fish oil; however, it contains at least 96% EPA and does not contain DHA. Studies suggest that this formulation does not cause significant increases in LDL-C, unlike the traditional mixtures of EPA and DHA.[6]

Familial hypercholesterolemia (FH) is a genetic disease caused by mutation of one or more of the genes critical for LDL-C catabolism and is characterized by high LDL-C since birth and a propensity to early onset atherosclerotic disease. FH is inherited as an autosomal dominant trait with heterozygotes less severely affected than homozygotes because homozygous familial hypercholesterolemia (HoFH) is usually characterized by loss-of-function mutations. Unlike HoFH, heterozygous familial hypercholesterolemia (HeFH) is a common genetic condition.[7,8]

Bempedoic acid (Nexletol®) is an adenosine triphosphate-citrate lyase (ACL) inhibitor that is FDA-approved as a monotherapy (Nexletol®) or a combination therapy with ezetimibe (Nexlizet®) for the treatment of HeFH.[9,10] Inhibition of ACL results in decreased cholesterol synthesis in the liver and lowers LDL-C in the blood via upregulation of LDL receptors.[9] Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine thus leading to a decrease in the delivery of intestinal cholesterol to the liver, reduction of hepatic cholesterol stores, and clearance of cholesterol from the blood.[10]

Lomitapide (Juxtapid®) is a microsomal triglyceride transfer protein inhibitor that can be used to treat HoFH. This inhibition prevents the assembly of apolipoprotein (apo) B-containing lipoproteins thus leading to reductions in VLDL synthesis and levels of plasma LDL-C.[11] Evinacumab-dgnb (Evkeeza®) is a monoclonal antibody that

inhibits angiopoietin-like protein 3 (ANGPTL3) that can also be used to treat HoFH. Inhibition of ANGPTL3 leads to reduction of LDL-C by promoting VLDL processing and clearance upstream of LDL formation as well as to reductions in TG and HDL-C by rescuing lipoprotein lipase and endothelial lipase activities, respectively.[12]

Leqvio® (inclisiran) is a first-in-class small interfering RNA directed to PCSK9 mRNA. It is FDA-approved for use as an adjunct to diet and statin therapy in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C. Leqvio® (inclisiran) is administered by a healthcare professional as a twice-yearly subcutaneous injection.[13]

There are over-the-counter (OTC) niacin products currently available, and these products are labeled as dietary supplements. While these supplements are "generally recognized as safe", the FDA does not examine the efficacy and safety of these products or regulate the manufacturing process.[14,15] The FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products "treat, cure, or prevent any disease". Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.[14] The American Heart Association states that "dietary supplement niacin must not be used as a substitute for prescription niacin because of potentially serious side effects".[16]

The miscellaneous antilipemic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Icosapent ethyl, niacin, and omega-3 acid ethyl esters are available in a generic formulation. This class was last reviewed in February 2022.

Table 1. Antilipemic Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Bempedoic acid	tablet	Nexletol®	none
Bempedoic acid and ezetimibe	tablet	Nexlizet®	none
Evinacumab-dgnb	injection	Evkeeza®	none
Icosapent ethyl	capsule	Vascepa®*	Vascepa®*
Inclisiran	injection	Leqvio®	none
Lomitapide	capsule	Juxtapid®	none
Niacin	extended-release tablet	Niaspan®*	niacin
Omega-3 acid ethyl esters	capsule	Lovaza®*	omega-3 acid ethyl esters

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antilipemic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antilipemic Agents, Miscellaneous

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[17]	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant,

Clinical Guideline	Recommendation
	ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)[1]**	<u>General recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant, or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Statins</u> • Statins should be considered as first-line drugs when LDL-lowering drugs are

Clinical Guideline	Recommendation
	indicated to achieve LDL treatment goals. Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout, and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. Omega-3 fatty acids • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Association of Clinical Endocrinologists/ American College of Endocrinology:	Cholesterol Goals • For patients at low risk for ASCVD (i.e., no risk factors), goals of LDL-C<130 mg/dL, non-HDL-C<160 mg/dL, and TG<150 mg/dL are recommended. • For patients at moderate risk for ASCVD (i.e., two or fewer risk factors and a calculated 10-year risk of <10%), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended.

Clinical Guideline	Recommendation
Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2017)[18] and Executive Summary (2020)[19]	• For patients at high risk for ASCVD (i.e., two or more risk factors and a 10-year risk between 10% and 20% or who have diabetes or stage ≥3 CKD with no other risk factors), goals of LDL-C<100 mg/dL, non-HDL-C<130 mg/dL, apo B<90 mg/dL, and TG<150 mg/dL are recommended. • For patients at very high risk for ASCVD (i.e., established clinical ASCVD or recent hospitalization for ACS, carotid or peripheral vascular disease, or 10-year risk >20%; diabetes with one or more risk factor(s); CKD stage 3 or higher with albuminuria; or HeFH), goals of LDL-C<70 mg/dL, non-HDL-C<100 mg/dL, apo B<80 mg/dL, and TG<150 mg/dL are recommended. • For individuals at extreme risk (i.e., progressive ASCVD including unstable angina that persists after achieving an LDL-C <70 mg/dL; established clinical ASCVD in individuals with diabetes, CKD stage 3 or higher, and/or HeFH); history of premature ASCVD (<55 years of age for males or <65 years of age for females), goals of LDL-C<55 mg/dL, non-HDL-C<80 mg/dL, apo B<70 mg/dL, and TG<150 mg/dL are recommended. • An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100 to 129 mg/dL considered "borderline" and 130 mg/dL or greater considered "high" (based on recommendations from the American Academy of Pediatrics). • Due to its potential cardioprotective role, HDL-C should be >40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C. <u>General Recommendations</u> • A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes and patient education with pharmacotherapy as needed to achieve evidence based targets. • A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include ≥30 minutes of moderate-intensity physical activity [consuming 4 to 7 kcal/min] four to six times weekly, with an expenditure of ≥200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities. • Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs. • In addition to aerobic activity, muscle-strengthening activity is recommended at least two days a week. • For adults, a reduced-calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains (primarily whole grains), fish, and lean meats is recommended. • For adults, the intake of saturated fats, trans-fats, and cholesterol should be limited, while LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10 to 25 g/day). • Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children. • Excessive alcohol intake should be avoided. • Tobacco cessation should be strongly encouraged and facilitated. • In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals.

Clinical Guideline	Recommendation
	Statins • Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. • For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction. • In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered. • Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, who also have at least one additional risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL. • Extreme risk individuals should be treated with statins to target an even lower LDL-C treatment goal of <55 mg/dL. Fibrates • Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). • Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add fibrate. • In patients treated with a statin and icosapent ethyl with TG≥150 mg/dL, a fibrate may be considered. Omega-3 Fish Oil • Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose. • Omega-3 should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add omega-3. Niacin • Niacin therapy is recommended principally as an adjunct for reducing TG. • Niacin therapy should not be used in individuals aggressively treated with statin due to absence of additional benefits with well-controlled LDL-C. • Niacin should be added as necessary if TG remains ≥500 mg/dL despite treatment with low fat diet, fibrates, and a statin. • In patients treated with statins who have TG<500 mg/dL, and no established ASCVD or diabetes with two or more ASCVD risk factors, consideration should be given to add niacin. • In patients treated with a statin and icosapent ethyl with TG>150 mg/dL, niacin may be considered. Icosapent Ethyl • Icosapent ethyl (two grams twice daily) should be added to a statin in any patient with established ASCVD or diabetes with two or more ASCVD risk factors and triglycerides between 135 to 499 mg/dL to prevent ASCVD events. Bile Acid Sequestrants

Clinical Guideline	Recommendation
	• Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG. <u>Cholesterol Absorption Inhibitors</u> • Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals. • Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk. <u>PCSK9 Inhibitors</u> • Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH. • PCSK9 inhibitors should be considered in patients with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals. <u>Combination Therapy</u> • Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal. <u>Special Considerations: Women</u> • Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient. • Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended. <u>Special Considerations: Children and Adolescents</u> • Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, and particularly for those satisfying the following criteria: o LDL-C ≥190 mg/dL o LDL-C ≥160 mg/dL and the presence of two or more cardiovascular risk factors, even after vigorous intervention o Family history of premature ASCVD (before 55 years of age), or o Having overweight, obesity, or other elements of the insulin resistance syndrome <u>Follow-up and Monitoring</u> • Reassess individuals' lipid status six weeks after therapy initiation and again at six-week intervals until the treatment goal is achieved. • While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals. • While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment. • More frequent lipid status evaluation is recommended in situations such as deterioration of diabetes control, use of a new drug known to affect lipid levels, progression of atherothrombotic disease, considerable weight gain, unexpected adverse change in any lipid parameter, development of a new ASCVD risk factor, or convincing new clinical trial evidence or guidelines that suggest stricter lipid goals.

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	• Liver transaminase levels should be measured before and three months after niacin or fibric acid treatment initiation because most liver abnormalities occur within 3 months of treatment initiation. Liver transaminase levels should be measured periodically thereafter (e.g., semiannually or annually). • Creatine kinase levels should be assessed and the statin discontinued, at least temporarily, when an individual reports clinically significant myalgias or muscle weakness on statin therapy.
American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/ American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update (2011)**[20]	<u>Lipid management</u> • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (2018)**[21]	<u>Top 10 messages to reduce risk of atherosclerotic cardiovascular disease through cholesterol management</u> • In all individuals, emphasize a heart-healthy lifestyle across the life course. • In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. ○ Clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin. • In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy. Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. • In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

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	• In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. • In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy. • In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 to 189 mg/dL (≥1.8 to 4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium (CAC). • Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement four to 12 weeks after statin initiation or dose adjustment, repeated every three to 12 months as needed. <u>Recommendations for Statin Therapy Use in Patients With ASCVD</u> • In patients who are 75 years of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. • In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels. • In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe. • In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost. • In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy. • In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences. • In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. • In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe. • In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (three to five years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events.

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	<u>Recommendations for primary severe hypercholesterolemia (LDL-C ≥190 mg/dL)</u> • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher, maximally tolerated statin therapy is recommended. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher, ezetimibe therapy is reasonable. • In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL, who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL, while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered. • In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. • In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher and who achieve an on-treatment LDL-C level of 130 mg/dL or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered. <u>Recommendations for patients with diabetes mellitus</u> • In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. <u>Primary prevention recommendations for adults 40 to 75 years of age with LDL levels 70 to 189 mg/dL</u> • In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more. • For the primary prevention of clinical ASCVD in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL, the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%). • Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision. • In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy. • In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND o If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); o If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥ 55 years of age; o If CAC score is 100 or higher or in the 75th percentile or higher, it is

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	reasonable to initiate statin therapy • In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin. • In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Recommendations for older adults</u> • In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL, initiating a moderate-intensity statin may be reasonable. • In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy. • In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL, it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy. <u>Recommendations for children and adolescents</u> • In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity. • In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C. • In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL or higher with a clinical presentation consistent with familial hypercholesterolemia (FH) and who do not respond adequately with three to six months of lifestyle therapy, it is reasonable to initiate statin therapy. • In children and adolescents with a family history of either early CVD or significant hypercholesterolemia, it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age two years to detect FH or rare forms of hypercholesterolemia. • In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia. • In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome. • In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of nine and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities. <u>Recommendations for hypertriglyceridemia</u> • In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides. • In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently

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	elevated triglyceride level as a factor favoring initiation or intensification of statin therapy. • In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy. • In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL, and especially fasting triglycerides ≥1000 mg/dL), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy. <u>Recommendations for statin safety and statin-associated side effects</u> • A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully. • In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors. • In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and SAMS, is recommended before initiation of treatment. • In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy. • In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss. • In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity. • In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks. • In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit. • Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS. • In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the**	<u>Statin treatment</u> • The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). • High-intensity statin therapy should be initiated or continued as first-line therapy

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Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)[22]	in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. • For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%. • Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects.

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	• Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present.
	• Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
	  o Multiple or serious comorbidities, including impaired renal or hepatic function.
	  o History of previous statin intolerance or muscle disorders.
	  o Unexplained alanine transaminase elevations >3 times upper limit of normal.
	  o Patient characteristics or concomitant use of drugs affecting statin metabolism.
	  o >75 years of age.
	• Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:
	  o History of hemorrhagic stroke.
	  o Asian ancestry.
	• Creatine kinase should not be routinely measured in individuals receiving statin therapy.
	• Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy.
	• During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.
	• Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy.
	• During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera).
	• Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL.
	• It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.
	• Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.
	• For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug).
	• It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm:
	  o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy.
	  o If unexplained severe muscle symptoms or fatigue develop during statin

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	therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.

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	• Higher-risk individuals include:
	  o Individuals with clinical ASCVD <75 years of age.
	  o Individuals with baseline LDL-C ≥190 mg/dL.
	  o Individuals 40 to 75 years of age with diabetes mellitus.
	  o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials.
	• In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
	
	<u>Non statin safety</u>
	• Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter.
	• Niacin should not be used if:
	  o Hepatic transaminase elevations are higher than two to three times upper limit of normal.
	  o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur.
	  o New-onset atrial fibrillation or weight loss occurs.
	• In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy.
	• To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to:
	  o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated.
	  o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms.
	  o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly.
	  o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses.
	• Bile acid sequestrants should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur.
	• A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter.
	• It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL.
	• It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur.
	• Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.
	• Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect.

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	• Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. • If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
American College of Cardiology/American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)[23]**	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss

Clinical Guideline	Recommendation
	if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction;

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	○ dietary potassium supplementation; ○ increased physical activity with a structured exercise program; and ○ limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2021)**[24]	<u>Drugs</u> • Currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins), fibrates, bile acid sequestrants, selective cholesterol absorption inhibitors (e.g. ezetimibe) and, more recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and bempedoic acid. Response to all therapy varies widely among individuals and therefore monitoring the effect on LDL-C levels is recommended. • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins also lower triglycerides, and may reduce pancreatitis risk.

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	• Statins should be used as the drugs of first choice in patients at increased risk of ASCVD. • Selective cholesterol absorption inhibitors (ezetimibe) should be considered as second-line therapy, either on top of statins when the therapeutic goal is not achieved, or when a statin cannot be prescribed. • Among patients in whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C levels when administered in combination with ezetimibe. • PCSK9 inhibitors also lower triglycerides, raise HDL-C and apolipoprotein A-I, and lower lipoprotein(a), although the relative contributions of these lipid modifications remain unknown. • PCSK9 inhibitors decrease LDL-C by up to 60%, either as monotherapy or in addition to the maximal statin dose or other lipid-lowering therapies (ezetimibe). • Fibrates are used primarily for triglyceride lowering and, occasionally, for increasing HDL-C. Evidence supporting the use of these drugs for CVD event reduction is limited and, given the strong evidence favoring statins, routine use of these drugs in CVD prevention is not recommended. In order to prevent pancreatitis, when triglycerides are >10 mmol/L (>900 mg/dL) they must be reduced not only by drugs but also by restriction of alcohol, treatment of DM, withdrawal of estrogen therapy, etc. In those rare patients with severe primary hypertriglyceridemia, specialist referral must be considered. <u>Recommendations for pharmacological low-density lipoprotein cholesterol lowering for those <70 years of age</u> • It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group. • If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. • For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered. • For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered. • If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may be considered. • If the goal is not achieved, statin combination with a bile acid sequestrant may be considered.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2021)**[25]	<u>Secondary Stroke Prevention</u> • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or transient ischemic attack (TIA) presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other clinical ASCVD. • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, and LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD. • Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2018 ACC/AHA cholesterol guidelines, which include lifestyle modifications, dietary recommendations, and medication

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	recommendations. Treatment of Hypertriglyceridemia • In patients with ischemic stroke or TIA with fasting TG 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL, on moderate or high-intensity statin, with HbA_{1c} <10%, and with no history of pancreatitis, AF, or severe heart failure, treatment with icosapent ethyl (IPE) 2 g twice a day is reasonable to reduce risk of recurrent stroke. • To further reduce the risk of ASCVD in patients with severe hypertriglyceridemia (>500 mg/dL), patients should implement a low-fat diet, avoid refined carbohydrates and alcohol, and consume omega-3 fatty acids.
American Association of the Study of Liver Disease: **Primary Biliary Cholangitis (2018)[26] and Update (2021)[27]**	• Ursodeoxycholic acid (UDCA) at a dose of 13 to 15 mg/kg/day is the first-line therapy for primary biliary cholangitis (PBC). • UDCA is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage. • For patients requiring bile acid sequestrants, UDCA should be given at least one hour before or four hours after the bile acid sequestrant. • Biochemical response to UDCA should be evaluated at 12 months after treatment initiation to determine whether patients should be considered for second-line therapy. • Obeticholic acid (OCA) was approved by the Food and Drug Administration in May 2016 to be used in combination with UDCA in patients with PBC who have inadequate response to at least one year of treatment with UDCA, or as monotherapy for those patients who are intolerant to UDCA. • Patients who are inadequate responders to UDCA should be considered for treatment with OCA, starting at 5 mg/day. • Fibrates can be considered as off-label alternatives for patients with PBC and inadequate response to UDCA, although fibrates are discouraged in patients with decompensated liver disease. • Use of OCA and fibrates is discouraged in patients with decompensated liver disease (Child-Pugh-Turcotte B or C). • OCA is contraindicated in patients with advanced cirrhosis, defined as cirrhosis with current or prior evidence of liver decompensation or portal hypertension. • Cholestyramine, colestipol, and colesevelam are nonabsorbable, highly positively charged resins that bind to negatively charged anions such as bile acids. It is not known which substance in the gut they may be binding to that leads to improved cholestatic itching, and clinical trials proving their efficacy are limited, but they have a long track record of clinical use.
National Institute for Health and Clinical Excellence: **Identification and management of familial hypercholesterolaemia (2008)[28]** **Last updated October 2019**	Drug treatment in adults • When offering lipid-modifying drug therapy to adults with familial hypercholesterolemia (FH), inform the patient that this treatment should be life-long. • Offer a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications or intolerance to initial statin therapy. • Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolemia who have been initiated on statin therapy when: ○ Serum total or LDL-C concentration is not appropriately controlled either

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	after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy AND o Consideration is being given to changing from initial statin therapy to an alternative statin. • Appropriate control of cholesterol concentrations should be based on individualized risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. • Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist center. • Offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). • Offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are at a very high risk of a coronary event [i.e., they have established coronary heart disease, a family history of premature coronary heart disease, or two or more other cardiovascular risk factors (e.g. they are male, they smoke, or they have hypertension or diabetes)]. • Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration. • The decision to offer treatment with a bile acid sequestrant (resin) or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH. • Exercise caution when adding a fibrate to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together. <u>Drug treatment in children and young people</u> • All children and young people diagnosed with, or being investigated for, a diagnosis of FH should have a referral to a specialist with expertise in FH in children and young people. • Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of ten years. The decision to defer or offer lipid-modifying drug therapy to a child or young person should take into account their age, the age of onset of coronary heart disease within the family, and the presence of other cardiovascular risk factors, including LCL-C concentration. • When offering lipid-modifying drug therapy for children or young people, inform the child/young person and their parent/caregiver that this treatment should be life-long. • Offer statins to children with FH by the age of ten years or at the earliest opportunity thereafter. • For children and young people with FH, consider a statin that is licensed for use in the appropriate age group. • Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group. • In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering: o A higher dose of statin than is licensed for use in the age group, and/or o More than one lipid-modifying drug therapy, and/or o Lipid-modifying drug therapy before the age of ten years. • In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy, and this should be considered before

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	LDL apheresis. • In children and young people with FH who are intolerant of statins, consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration [such as bile acid sequestrants (resins), fibrates, or ezetimibe]. • Routine monitoring of growth and pubertal development in children and young people with FH is recommended.
American College of Cardiology: **Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2022)**[29]	• Provides recommendations for situations not covered by the 2018 ACC/AHA cholesterol guidelines and for whether or when to use non-statin therapies if response to statins is deemed inadequate. • For all patient groups, lifestyle modification (adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) is a critical component of ASCVD risk reduction. The clinician-patient discussion regarding the addition of a non-statin medication to the current medication regimen should address the potential for net ASCVD risk reduction, safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering, cost, convenience, and medication storage, pill burden, frequency and route of administration, potential to jeopardize adherence to evidence-based therapies and patient preference. <u>Adults With Clinical ASCVD on Statin Therapy for Secondary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider LDL apheresis under care of lipid specialist if baseline LDL-C ≥190 mg/dL not due to secondary causes without clinical or genetic diagnosis of familial hypercholesterolemia. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH under care of lipid specialist, if at very high risk and baseline LDL-C ≥190 mg/dL not due to secondary causes with clinical diagnosis or genetic confirmation of familial hypercholesterolemia. <u>Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Primary Prevention</u> • Consider ezetimibe and/or PCSK9 inhibitor. • May consider bempedoic acid or inclisiran. • May consider evinacumab, lomitapide and/or LDL apheresis for HoFH.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antilipemic agents 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 3.1. FDA-Approved Indications for the Antilipemic Agents, Miscellaneous A-I[2,3,6,9,10,12,13]

Indication	Bempedoic acid	Bempedoic acid/ ezetimibe	Evinacumab-dgnb	Icosapent Ethyl*	Inclisiran
Hypertriglyceridemia					
Adjunct to diet to reduce triglyceride (TG) levels in adults with severe (≥500 mg/dL) hypertriglyceridemia				✔	
Secondary Prevention of Cardiovascular Disease					
Adjunct to diet and maximally tolerated statin therapy in patients with atherosclerotic cardiovascular disease	✔	✔			

who require additional lowering of LDL-C					
Adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (≥150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular use				✔	
Heterozygous Familial Hypercholesterolemia (HeFH)					
Adjunct to diet and maximally tolerated statin therapy in patients with HeFH or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C	✔	✔			
Adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including HeFH, to reduce LDL-C					✔
Homozygous Familial Hypercholesterolemia (HoFH)					
Adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients, aged 5 years and older, with HoFH			✔		

*Over-the-counter products are considered dietary supplements.

Table 3.2. FDA-Approved Indications for the Antilipemic Agents, Miscellaneous Continued, L-Z[2-5,11]

Indication	Lomitapide	Niacin Extended Release*	Omega-3 Acid Ethyl Esters*
Hypertriglyceridemia			
Adjunctive therapy for the treatment of adult patients with severe hypertriglyceridemia who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them		✔	
Adjunct to diet to reduce triglyceride (TG) levels in adults with severe (≥500 mg/dL) hypertriglyceridemia			✔
Primary Hypercholesterolemia and Mixed Dyslipidemia			
Adjunct to diet to reduce elevated TC, LDL-C, apolipoprotein B, and TG levels, and to increase high-density lipoprotein cholesterol in patients with primary hyperlipidemia and mixed dyslipidemia		✔	
Adjunct to diet and in combination with a bile acid binding resin to reduce elevated TC and LDL-C levels in adult patients with primary hyperlipidemia		✔	
Secondary Prevention of Cardiovascular Disease			
Adjunct to diet to reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia		✔	
Adjunct to diet and in combination with a bile acid binding resin to slow progression or promote regression of atherosclerotic disease in patients with a history of		✔	

coronary artery disease and hyperlipidemia			
Homozygous Familial Hypercholesterolemia (HoFH)			
Adjunct to low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, TC, apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with HoFH	✔		

*Over-the-counter products are considered dietary supplements.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antilipemic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antilipemic Agents, Miscellaneous[2-6,9-13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Bempedoic Acid	Not reported	99.3	Liver (% not reported)	Feces (30) Urine (70)	21 hours
Bempedoic acid/ Ezetimibe	Not reported/ 35 to 60	99.3/ >90	Liver (% not reported)	Feces 30/78 Urine 70/11	21 hours/ 22 hours
Evinacumab-dgnb	Not reported	Not reported	Not reported	Renal (unlikely)	Not reported
Icosapent ethyl	Not reported	>99	Liver (% not reported)	Not reported	89 hours
Inclisiran	Not reported	87%	Metabolized by nucleases	Renal (16)	9 hours
Lomitapide	7	99.8	Liver (extensive)	Renal (53 to 60) Feces (33 to 35)	39.7 hours
Niacin	60 to 76	< 20%	Liver (rapid; % not reported)	Renal (60 to 88)	20 to 45 minutes
Omega-3 acid ethyl esters	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Major drug interactions with the miscellaneous antilipemic agents are listed in Table 5. There are no significant drug interactions reported with evinacumab-dgnb, icosapent ethyl, inclisiran, niacin, and omega-3 acid ethyl esters.[2] Concomitant use of bempedoic acid and pravastatin or simvastatin is not recommended due to the increased risk of myopathy and other statin medications should be considered. This interaction also applies to the combination product bempedoic acid/ezetimibe; however, is not listed in the table twice.

Table 5. Major Drug Interactions with the Antilipemic Agents[3]

Generic Name(s)	Interaction	Mechanism
Bempedoic acid	Pravastatin	Concurrent use of bempedoic acid and pravastatin may result in increased concentration of pravastatin and may increase the risk of myopathy.
Bempedoic acid	Simvastatin	Concurrent use of bempedoic acid and simvastatin may result in increased concentration of simvastatin and may increase the risk of myopathy.
Bempedoic acid/ ezetimibe	Cyclosporine	Concurrent use of ezetimibe and cyclosporine increases ezetimibe ad cyclosporine concentrations and risk of adverse reactions (e.g., nephrotoxicity).

Generic Name(s)	Interaction	Mechanism
Bempedoic acid/ ezetimibe	Fibrates	Concurrent use of ezetimibe and fibrates may result in increased ezetimibe concentrations and an increased risk of cholelithiasis.
Lomitapide	Bile Acid Sequestrants	Lomitapide has not been tested for interaction with bile acid sequestrants. Administration of lomitapide and bile acid sequestrants should be separated by at least four hours since bile acid sequestrants can interfere with the absorption of oral medications.
Lomitapide	HMG-CoA Reductase Inhibitors (atorvastatin, lovastatin, simvastatin)	Inhibition of metabolism (CYP3A4) of certain HMG-CoA reductase inhibitors by lomitapide. Plasma concentrations of certain HMG-CoA reductase inhibitors may be elevated, increasing the pharmacologic effects and risk of adverse reactions (e.g., myositis).
Lomitapide	Moderate CYP3A4 Inhibitors	Although concomitant use with moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) has not been studied, concomitant used with lomitapide is contraindicated because lomitapide exposure will likely increase significantly in the presence of these inhibitors.
Lomitapide	Strong CYP3A4 Inhibitors	Concomitant use of strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole) with lomitapide is contraindicated. Strong CYP3A4 inhibitors have been shown to increase lomitapide exposure approximately 27-fold. Patients must avoid grapefruit juice while taking lomitapide.
Lomitapide	P-glycoprotein Substrates	Lomitapide is an inhibitor of P-glycoprotein (P-gp). Coadministration of lomitapide with P-gp substrates (such as aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan) may increase the absorption of P-gp substrates. Dose reduction of the P-gp substrate should be considered when used concomitantly with lomitapide.
Lomitapide	Weak CYP3A4 Inhibitors	When administered with weak CYP3A4 inhibitors (e.g., alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, pazopanib, ranitidine, ranolazine, ticagrelor, zileuton), the dose of lomitapide should be decreased in half because weak CYP3A4 inhibitors can increase lomitapide exposure approximately two-fold. Do not exceed 30 mg daily of lomitapide when used concomitantly with weak CYP3A4 inhibitors except when coadministered with oral contraceptives, in which case the maximum recommended lomitapide dose is 40 mg daily.
Lomitapide	Warfarin	Lomitapide increases plasma concentrations of both R(+)-warfarin and S(-)-warfarin by approximately 30% and increased the INR 22%. Patients taking warfarin should undergo regular monitoring of INR, particularly after any changes in lomitapide dosage. The dose of warfarin should be adjusted as clinically indicated.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antilipemic agents are listed in Table 6. The boxed warning for lomitapide is listed in Table 7. Pooled data from randomized, placebo-controlled trials have shown that prescription omega-3 acid ethyl esters are safe and well tolerated.[14] At usual antilipemic dosages, niacin is generally well tolerated and side effects are mild and transient. The most common adverse effects with niacin are gastrointestinal upset, flushing, and pruritus. Flushing may be diminished by starting with a low dose, taking niacin after meals, and by pretreating with aspirin or ibuprofen.[2,3] Sustained-release preparations have been shown to be hepatotoxic in doses ≥2 g per day. Adverse events for bempedoic acid/ezetimibe were reported individually for each agent per package insert. The most common adverse effects with bempedoic acid are upper respiratory infection, pain, and muscle spasms.[9] Upper respiratory infections, myalgia, and diarrhea are the most common adverse effects associated with ezetimibe.[10] The most common adverse effects reported with evinacumab are nasopharyngitis, dizziness, and nausea.[12]

Table 6. Adverse Drug Events (%) Reported with the Antilipemic Agents, Miscellaneous[2-6,9-13]

Adverse Event	Bempedoic acid	Ezetimibe	Evinacumab-dgnb	Icosapent Ethyl	Inclisiran	Lomitapide	Niacin ER	Omega-3 Acid Ethyl Esters
Cardiovascular								
Angina pectoris	-	-	-	-	-	10	-	1
Arrhythmia	-	-	-	-	-	-	✔	✔
Atrial fibrillation	1.7	-	-	✔	-	-	✔	-
Bypass surgery	-	-	-	-	-	-	-	✔
Cardiac arrest	-	-	-	-	-	-	-	✔
Chest pain	-	-	-	-	-	24	-	✔
Hypertension	-	-	-	-	-	-	-	✔
Hypotension	-	-	-	-	-	-	✔	-
Migraine	-	-	-	-	-	-	✔	✔
Myocardial infarction	-	-	-	-	-	-	-	✔
Myocardial ischemia	-	-	-	-	-	-	-	✔
Occlusion	-	-	-	-	-	-	-	✔
Orthostasis	-	-	-	-	-	-	✔	-
Palpitations	-	-	-	-	-	10	✔	-
Peripheral edema	-	-	-	✔	-	-	✔	-
Peripheral vascular disorder	-	-	-	-	-	-	-	✔
Postural hypotension	-	-	-	-	-	-	✔	-
Syncope	-	-	-	-	-	-	✔	✔
Tachycardia	-	-	-	-	-	-	✔	✔
Central Nervous System								
Depression	-	-	-	-	-	-	-	✔
Dizziness	-	✔	6	-	-	10	✔	✔
Emotional lability	-	-	-	-	-	-	-	✔
Facial paralysis	-	-	-	-	-	-	-	✔
Fatigue	-	0.2 to 4	-	-	-	17	-	-
Headache	-	-	-	-	-	10	✔	-
Insomnia	-	-	-	-	-	-	✔	✔
Migraine	-	-	-	-	-	-	✔	-
Nervousness	-	-	-	-	-	-	✔	-
Paresthesia	-	-	-	-	-	-	✔	-
Vasodilatation	-	-	-	-	-	-	-	✔
Vertigo	-	-	-	-	-	-	-	✔
Dermatologic								
Acanthosis nigricans	-	-	-	-	-	-	✔	-
Alopecia	-	-	-	-	-	-	-	✔
Dry skin	-	-	-	-	-	-	✔	-
Eczema	-	-	-	-	-	-	-	✔
Flushing	-	-	-	-	-	-	63 to 69	-

Adverse Event	Bempedoic acid	Ezetimibe	Evinacumab-dgnb	Icosapent Ethyl	Inclisiran	Lomitapide	Niacin ER	Omega-3 Acid Ethyl Esters
Hyperpigmentation	-	-	-	-	-	-	-	-
Pruritus	-	-	-	-	-	-	3 to 8	✔
Rash	-	-	-	-	-	-	0 to 5	2
Skin burning sensation	-	-	-	-	-	-	✔	-
Skin discoloration	-	-	-	-	-	-	✔	-
Sweating	-	-	-	-	-	-	✔	-
Urticaria	-	-	-	-	-	-	✔	✔
Endocrine and Metabolic								
Gout	1.5		-	✔	-	-	✔	-
Gastrointestinal								
Abdominal discomfort	3.1	-	-	✔	-	21	-	-
Abdominal pain	3.1	-	✔	-	-	34	-	-
Abdomen enlarged	-	-	-	-	-	21	-	✔
Anorexia	-	-	-	-	-	-	-	✔
Colitis	-	-	-	-	-	-	-	✔
Constipation	-	-	✔	✔	-	21	-	✔
Defecation urgency	-	-	-	-	-	10	-	-
Diarrhea	-	2.5 to 4.1	-	✔	-	79	7 to 14	-
Dry mouth	-	-	-	-	-	-	-	✔
Dyspepsia	-	-	-	-	-	38	✔	3
Dysphagia	-	-	-	-	-	-	-	✔
Eructation	-	-	-	-	-	-	✔	5
Fecal incontinence	-	-	-	-	-	-	-	✔
Flatulence	-	-	-	-	-	21	✔	-
Gastritis	-	-	-	-	-	-	-	✔
Gastroenteritis	-	-	-	-	-	14	-	✔
Gastroesophageal reflux disease	-	-	-	-	-	10	-	-
Increased appetite	-	-	-	-	-	-	-	✔
Intestinal obstruction	-	-	-	-	-	-	-	✔
Melena	-	-	-	-	-	-	-	✔
Nausea	-	-	5	-	-	65	4 to 11	-
Pancreatitis	-	-	-	-	-	-	-	✔
Peptic ulceration	-	-	-	-	-	-	✔	-
Tenesmus	-	-	-	-	-	10	-	✔
Vomiting	-	-	-	-	-	34	0 to 9	✔
Weight loss	-	-	-	-	-	24	-	-
Hematologic								
Anemia	2.8	-	-	-	-	-	-	-
Bleeding	-	-	-	12	-	-	-	-
Leukopenia	9	-	-	-	-	-	-	-
Prothrombin time increased	-	-	-	-	-	-	✔	-
Thrombocythemia	10	-	-	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	-	✔	-
Hepatic								
Fulminant hepatic necrosis	-	-	-	-	-	-	✔	-
Hepatitis	-	-	-	-	-	-	✔	-
Hepatotoxicity	-	-	-	-	-	10	✔	-
Jaundice	-	-	-	-	-	-	✔	-
Laboratory Test Abnormalities								
Amylase increased	-	-	-	-	-	-	✔	-
Hepatic steatosis	-	-	-	-	-	78	-	-
Hyperglycemia	-	-	-	-	-	-	✔	✔
Hyperlipidemia	-	-	-	-	-	-	-	✔

Adverse Event	Bempedoic acid	Ezetimibe	Evinacumab-dgnb	Icosapent Ethyl	Inclisiran	Lomitapide	Niacin ER	Omega-3 Acid Ethyl Esters
Hyperuricemia	3.5	-	-	-	-	-	✔	-
Lactate dehydrogenase increased	-	-	-	-	-	-	✔	-
Liver function test abnormalities	2.1	0.5 to 3	-	-	-	34	✔	✔
Phosphorus decreased	-	-	-	-	-	-	✔	-
Triglycerides increased	-	-	-	✔	-	-	-	-
Musculoskeletal								
Arthralgia	-	2.6 to 3	-	2.3	5	-	-	✔
Arthritis	-	-	-	-	-	-	-	✔
Asthenia	-	-	4	-	-	-	✔	✔
Back pain	3.3	-	-	-	-	14	-	2
Extremities pain	-	2.7 to 3	4	✔	-	-	-	-
Fracture	-	-	-	-	-	-	-	✔
Malaise	-	-	-	-	-	-	-	✔
Muscle spasm	3.6	-	-	-	-	-	-	-
Myalgia	-	3.2	-	-	-	-	✔	✔
Myasthenia	-	-	-	-	-	-	✔	-
Myopathy	-	✔	-	-	-	-	✔	-
Neck pain	-	-	-	-	-	-	-	✔
Pain	3	-	-	✔	-	-	-	2
Rhabdomyolysis	-	✔	-	-	-	-	✔	-
Rheumatoid arthritis	-	-	-	-	-	-	-	✔
Tendon rupture	0.5	-	-	-	-	-	-	✔
Respiratory								
Asthma	-	-	-	-	-	-	-	✔
Bronchitis	3	-	-	-	4	-	-	✔
Cough	-	-	-	-	-	-	2 to 8	✔
Dyspnea	-	-	-	-	-	-	✔	✔
Epistaxis	-	-	-	-	-	-	-	✔
Influenza	-	2	-	-	-	-	-	-
Laryngitis	-	-	-	-	-	-	-	✔
Nasal congestion	-	-	✔	-	-	10	-	-
Pharyngitis	-	3.7	16	✔	-	17	-	✔
Pneumonia	-	-	-	-	-	-	-	✔
Rhinitis	-	-	5	-	-	-	-	✔
Sinusitis	-	2.8	-	-	-	-	-	✔
Upper respiratory infection	4.5	2.9 to 4.3	✔	-	-	-	-	-
Urogenital								
Benign Prostatic Hyperplasia	1.3	-	-	-	-	-	-	-
Cervix disorder	-	-	-	-	-	-	-	✔
Endometrial carcinoma	-	-	-	-	-	-	-	✔
Epididymitis	-	-	-	-	-	-	-	✔
Impotence	-	-	-	-	-	-	-	✔
Other								
Anaphylaxis	-	-	-	-	-	-	✔	✔
Angioedema	-	-	-	-	-	-	✔	-
Antibody development	-	-	-	-	5	-	-	-
Blurred vision	-	-	-	-	-	-	✔	-
Body odor	-	-	-	-	-	-	-	✔
Cataract	-	-	-	-	-	-	-	✔

Adverse Event	Bempedoic acid	Ezetimibe	Evinacumab-dgnb	Icosapent Ethyl	Inclisiran	Lomitapide	Niacin ER	Omega-3 Acid Ethyl Esters
Chills	-	-	-	-	-	-	✔	✔
Edema	-	-	-	-	-	-	-	✔
Facial edema	-	-	-	-	-	-	✔	-
Fever	-	-	-	-	-	10	-	✔
Flu symptoms	-	-	7	-	-	21	-	4
Hemorrhagic diathesis	-	-	-	-	-	-	-	✔
Hypersensitivity reactions	-	-	1	-	-	-	✔	-
Infection	-	-		-	-	-	-	4
Injection-site reaction	-	-	7	-	8	-	-	-
Laryngismus	-	-	-	-	-	-	✔	-
Larynx edema	-	-	-	-	-	-	✔	-
Lymphadenopathy	-	-	-	-	-	-	-	✔
Macular edema	-	-	-	-	-	-	✔	-
Neoplasm	-	-	-	-	-	-	-	✔
Psychiatric disorders	-	-	-	-	-	-	-	-
Sudden death	-	-	-	-	-	-	-	✔
Suicide	-	-	-	-	-	-	-	✔
Taste perversion	-	-	-	-	-	-	-	3
Tongue edema	-	-	-	-	-	-	✔	-
Toxoid amblyopia	-	-	-	-	-	-	✔	-
Vascular disorders	-	-	-	-	-	-	-	-

✔ Percent not specified.
-Event not reported.
ER=Extended-release,

Table 7. Boxed Warning for Lomitapide[8]

WARNING
Warning: Risk of Hepatotoxicity Lomitapide can cause elevations in transaminases. In the Juxtapid clinical trial, 10 (34%) of the 29 patients treated with lomitapide had at least one elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase. Lomitapide also increases hepatic fat, with or without concomitant increases in transaminases. The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% at baseline, measured by magnetic resonance spectroscopy. Hepatic steatosis associated with lomitapide treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended. During treatment, adjust the dose of lomitapide if the ALT or AST are ≥3x ULN. Discontinue lomitapide for clinically significant liver toxicity. Because of the risk of hepatotoxicity, lomitapide is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the JUXTAPID REMS Program. Prescribe lomitapide only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of lomitapide have not been established in patients with hypercholesterolemia who do not have HoFH.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antilipemic agents are listed in Table 8.

Table 8. Usual Dosing Regimens for the Antilipemic Agents, Miscellaneous[2-6,9-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Bempedoic acid	Atherosclerotic cardiovascular disease: Tablet: 180 mg once daily Heterozygous Familial Hypercholesterolemia: Tablet: 180 mg once daily	Safety and effectiveness in children have not been established.	Tablet: 180 mg
Bempedoic acid/ezetimibe	Atherosclerotic cardiovascular disease: Tablet: 180 mg/10 mg once daily Heterozygous Familial Hypercholesterolemia: Tablet: 180 mg/10 mg once daily	Safety and effectiveness in children have not been established.	Tablet: 180 mg/10 mg
Evinacumab-dgnb	Homozygous Familial Hypercholesterolemia: Injection: 15 mg/kg administered by intravenous (IV) infusion over 60 minutes once monthly	Safety and effectiveness in children ≤5 years have not been established. Homozygous Familial Hypercholesterolemia: Injection: 15 mg/kg administered by intravenous (IV) infusion over 60 minutes once monthly	Vial: 345 mg/2.3 mL (150 mg/mL) 1,200 mg/8 mL (150 mg/mL)
Icosapent ethyl	Severe hypertriglyceridemia: Capsule: 4 g/day taken as four 0.5 gram capsules twice daily or two 1 gram capsules twice daily	Safety and effectiveness in children have not been established.	Capsule: 0.5 gram 1 gram
Inclisiran	Heterozygous Familial Hypercholesterolemia and secondary prevention of ASCVD: Injection: 284 mg administered as a single subcutaneous injection, again at 3 months, and then every 6 months thereafter	Safety and effectiveness in children have not been established.	Injection: 284 mg/ 1.5 mL
Lomitapide	Homozygous Familial Hypercholesterolemia*: Capsule: initial, 5 mg once daily; maximum, 60 mg once daily	Safety and effectiveness in children have not been established.	Capsule: 5 mg 10 mg 20 mg 30 mg
Niacin	Hyperlipidemia: Extended-release tablet: initial, 500 mg at bedtime; maintenance, 1,000 to 2,000 mg once daily; maximum, doses >2,000 mg/day are not recommended Secondary prevention of cardiovascular disease: Extended-release tablet: initial, 500 mg	Safety and efficacy in children have not been established (extended-release capsule, immediate-release). Safety and effectiveness in children ≤16 years of age have not been established	Extended-release tablet: 500 mg 750 mg 1,000 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	at bedtime; maintenance, 1,000 to 2,000 mg once daily; maximum, doses >2,000 mg/day are not recommended Severe hypertriglyceridemia: Extended-release tablet: initial, 500 mg at bedtime; maintenance, 1,000 to 2,000 mg once daily; maximum, doses >2,000 mg/day are not recommended	(extended-release tablet).	
Omega-3 acid ethyl esters	Severe hypertriglyceridemia: Capsule: 4 g/day taken as a single 4 g dose or as two 2 g doses (2 capsules given twice daily)	Safety and effectiveness in children have not been established.	Capsule: 1 gram

*Before beginning treatment, measure alanine aminotransaminase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antilipemic agents are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Antilipemic Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hyperlipidemia				
Goldberg et al.[31] (2019) CLEAR Wisdom Bempedoic acid 180 mg daily vs placebo daily	DB, PC, RCT Patients >18 years old with atherosclerotic cardiovascular disease or risk and/or HeFH who had been receiving stable, maximally tolerated lipid-lowering therapy and had a fasting LDL-C >70 mg/dL	N=779 1 week screening period 4-week placebo run-in phase 52 weeks of treatment	Primary: Percent-change from baseline to week 12 in LDL-C level Secondary: Percent change from baseline to week 24 in LDL-C and to week 12 in non-HDL-C, TC, apo B, hsCRP	Primary: At week 12 the percent-change from baseline LDL-C was -15.1% vs. 2.4%; P<0.001, for bempedoic acid and placebo, respectively. Secondary: Percent change from baseline LDL-C at week 24 was -12.1% vs 2.7%; P<0.001, for bempedoic acid and placebo respectively. Significant percent change reductions were also seen at week 12 between bempedoic acid and placebo for non-HLD-C (-10.8% vs 2.3%; P<0.001, respectively), TC (-9.9% vs 1.3%; P<0.001, respectively), apo B (-9.3% vs 3.7%; P<0.001, respectively), and hsCRP (-18.7% vs –9.4%; P=0.04, respectively). The incidence of adverse events was generally similar across the two groups.
Laufs et al.[32] (2019) CLEAR Serenity Bempedoic acid 180 mg daily vs placebo daily	DB, PC, PG, RCT Patients >18 years old receiving lipid modifying therapy for primary or secondary prevention of CV events with fasting LDL-C >130 mg/dL. Patients with HeFH with LDL-C >100 mg/dL. All patients had a history of statin intolerance.	N=345 1 week screening period 4-week placebo run-in phase 24 weeks of treatment	Primary: Percent change from baseline to week 12 in LDL-C Secondary: Percent change from baseline to week 24 in LDL-C and to week 12 in non-HDL-C, TC, apo B, hsCRP, TG, and HDL-C	Primary: At week 12 the percent-change from baseline LDL-C was -23.6% vs -1.3%; P<0.001 for bempedoic acid and placebo, respectively. Secondary: Percent change from baseline LDL-C at week 24 was -21.2% vs -2.3%; P<0.001, for bempedoic acid and placebo, respectively. Significant percent change reductions were also seen at week 12 between bempedoic acid and placebo for non-HLD-C (-18.0% vs –0.9%; P<0.001, respectively), TC (-15.5% vs –1.0%; P<0.001, respectively), apo B (-15.0% vs 0.5%; P<0.001, respectively), hsCRP (-25.1% vs 4.4%; P<0.001, respectively), TG (7.9% vs 7.4%; P=0.921, respectively), and HDL-C (-5.2% vs –0.6%; P=0.003, respectively). Treatment-emergent adverse events occurred in 64.1% and 56.8% of patients in the bempedoic acid and placebo treatment groups, respectively

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ray et al.[33] (2019) CLEAR Harmony Bempedoic acid 180 mg daily vs placebo daily	DB, PC, PG, RCT Patients >18 years old with atherosclerotic cardiovascular disease and/or HeFH on stable doses of maximally tolerated statin therapy with fasting LDL-C >70 mg/dL	N=345 2 week screening period 4-week placebo run-in phase 52 weeks of treatment	Primary: Overall safety according to adverse events and changes in safety laboratory variables Secondary: Percent change from baseline to week 12 in LDL-C, non-HDL-C, TC, apo B, hsCRP	Primary: The incidence of adverse events bempedoic acid group vs placebo was 78.5% vs 78.7%; P=0.91, respectively, with most events being mild to moderate. The incidence of serious adverse events was similar with 14.5% vs 14.0%; P=0.80 for bempedoic acid and placebo, respectively. More patients in the bempedoic acid group discontinued compared to placebo (10.9% vs 7.1%; P=0.005, respectively). Secondary: The bempedoic acid group had significant percent change reductions compared to placebo in LDL-C (-16.5% vs 1.6%; P<0.001, respectively), non-HDL-C (-11.9% vs 1.5%; P<0.001, respectively), TC (-10.3% vs 0.8%; P<0.001, respectively), apo B (-8.6% vs 3.3%; P<0.001, respectively), and hsCRP (-22.4% vs 2.6%; P<0.001, respectively) at week 12.
Ballantyne et al.[34] (2018) Bempedoic acid 180 mg and ezetimibe 10 mg daily vs placebo and ezetimibe 10mg	DB, PC, PG, RCT Patients >18 years old who had a history of statin intolerance and required additional LDL-C lowering with fasting LDL-C >100 mg/dL	N=269 1 week screening period 4-week ezetimibe 10 mg + placebo run-in phase 12 weeks of bempedoic acid 180 mg vs placebo	Primary: Percent-change from baseline to week 12 in LDL-C Secondary: Percent change from baseline to week 12 non-HDL-C, TC, apo B, hsCRP, TG, and HDL-C	Primary: At week 12 the percent-change from baseline LDL-C was -23.5% vs 5.0%; P<0.001, for bempedoic acid/ezetimibe and placebo/ezetimibe, respectively. Secondary: Significant percent change reductions were seen at week 12 between bempedoic acid/ezetimibe and placebo for non-HLD-C (-18.4% vs 5.2%; P<0.001, respectively), TC (-15.1% vs 2.9%; P<0.001, respectively), apo B (-14.6% vs 4.7%; P<0.001, respectively), and hsCRP (-32.5% vs 2.1%; P<0.001, respectively).
Ballantyne et al.[35] (2020) Bempedoic acid/ezetimibe 180 mg/10 mg daily	DB, MC, PC, RCT Patients >18 years old with high CVD risk due to atherosclerotic	N=382 12 weeks	Primary: Percent-change from baseline to week 12 in LDL-C and comparison of the three treatment	Primary: At week 12, LDL-cholesterol lowering with bempedoic acid/ezetimibe was significantly greater than that for the placebo, ezetimibe, or bempedoic acid groups (-36.2%, 1.8%, -23.2%, -17.2%; P<0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs bempedoic acid 180 mg daily vs ezetimibe 10 mg daily vs placebo daily	cardiovascular disease and/or HeFH on stable doses of maximally tolerated statin therapy with fasting LDL-C >100 mg/dL		arms Secondary: Percent change from baseline to week 12 in non-HDL-C, TC, apo B, hsCRP	Secondary: At week 12 the percent change from baseline for bempedoic acid/ezetimibe, placebo, ezetimibe, and bempedoic acid groups: • non-HDL-C (-31.9%, 1.8%, -19.9%, -14.1%; P< 0.001, respectively) • TC (-26.4%, 0.7%, -16.0%, -12.1%; P<0.001, respectively) • Apo B (-24.6%, 5.5%, -15.3%, -11.8%; P<0.001, respectively) • hsCRP (-35.1%, 21.6%, -8.2%, -31.9%; P<0.001, respectively)
Raal et al.[36] (2020) ELIPSE HoFH Evinacumab 15 mg/kg every 4 weeks vs placebo every 4 weeks	DB, ES, MC, PC, PG, OL, RCT Patients ≥12 years with HoFH who were receiving stable lipid-lowering therapy at the maximum dose and were willing to consistently maintain his/her usual low fat or heart-healthy diet for the duration of the study (If undergoing low density lipoprotein apheresis, patients must have must have initiated low density lipoprotein apheresis at least 3 months prior to screening and be on a stable	N=65 24 weeks	Primary: Percent change from baseline to week 24 in LDL-C Secondary: Percent change from baseline to week 24 in apo B, non-HDL-C, and TC; proportion of patients with ≥30% reduction in LDL-C at week 24; proportion of patients with ≥50% reduction in LDL-C at week 24; proportion of patients with LDL-C <100 mg/dL at week 24, absolute change in	Primary: The percent change from baseline to week 24 in LDL-C was -47.1% for the evinacumab treatment group and +1.9% in the placebo group. The between group least-squares mean difference was -49.0 percentage points (95% CI, -65.0 to -33.1; P<0.001). The between group least-squares mean absolute difference in LDL-C was -132.1 mg/dL (95% CI, -175.3 to -88.9; P<0.001). Secondary: The percent change from baseline to week 24 in apo B was -41.4% in the evinacumab treatment group and -4.5% in the placebo group (least-squares mean difference, -36.9 percentage points; 95% CI, -48.6 to -25.2; P<0.001). The percent change from baseline to week 24 in non-HDL-C was -49.7% in the evinacumab treatment group and +2.0% in the placebo group (least-squares mean difference, -51.7 percentage points; 95% CI, -64.8 to -38.5; P<0.001). The percent change from baseline to week 24 in TC was -47.4% in the evinacumab treatment group and +1.0% in the placebo group (least-squares mean difference, -48.4 percentage points; 95% CI, -58.7 to -38.1; P<0.001). At week 24, 84% of patients treated with evinacumab had a ≥30% reduction in LDL-C compared with 18% of patients treated with placebo (OR, 25.2; P<0.0001). At week 24, the absolute change in calculated LDL-C was -134.7 mg/dL for the evinacumab group compared with -2.6 mg/dL for the placebo group (least-

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	schedule)		calculated LDL-C from baseline to week 24	squares mean difference, -132.1; 95% CI, -175.3 to -88.9; P<0.001). No other statistically significant differences between the evinacumab group and the placebo group were observed with respect to secondary endpoints.
Bays et al.[37] (2011) MARINE Icosapent ethyl 4 g/day (2 g twice daily) vs icosapent ethyl 2 g/day (1 g twice daily) vs placebo twice daily (Icosapent ethyl is referred to by the investigational name AMR101 in this trial)	DB, MC, PC, RCT Adults >18 years of age with TG levels of ≥500 and ≤2000 mg/dL	N=229 4 to 6 week wash-out (any lipid-altering drug therapy other than statins and ezetimibe were discontinued) 2 to 3 week qualifying period 12 weeks of treatment	Primary: Placebo-corrected median percentage of change in TG from baseline to week 12 Secondary: Percent change from baseline in VLDL-C, apo B, and lipoprotein-associated phospholipase A_2; safety	Primary: Icosapent ethyl 4 g/day reduced placebo-corrected median TG levels by 33.1% (P<0.0001); icosapent ethyl 2 g/day reduced placebo-corrected median TG levels by 19.7% (P=0.0051). Secondary: Neither icosapent ethyl 4 g/day nor 2 g/day significantly increased the LDL cholesterol levels. Icosapent ethyl 4 g/day significantly reduced non-HDL-C by 17.7% (P<0.0001), lipoprotein-associated phospholipase A_2 by 13.6% (P=0.0003), very low density lipoprotein–TG by 25.8% (P=0.0023), and apo B by 8.5% (P=0.0019). Icosapent ethyl 2 g/day significantly reduced non-HDL-C by 8.1% (P=0.0182). Both icosapent ethyl doses significantly reduced VLDL-C and TC, with no significant effect on HD-C. The incidence of treatment-emergent adverse events was generally similar across the three treatment groups.
Ballantyne et al.[38] (2012) ANCHOR Icosapent ethyl 4 g/day (2 g twice daily) vs icosapent ethyl 2	DB, MC, PC, RCT Patients >18 years of age and at high risk for CV disease with residually high TG levels (≥200 and <500 mg/dL) despite LDL-C control (≥40 and <100 mg/dL) with statin therapy	N=702 4 to 6 week wash-out (any lipid-altering drug therapy other than statins were discontinued)	Primary: Median percent change in TG levels from baseline versus placebo at 12 weeks Secondary: Median placebo-adjusted percent	Primary: Icosapent ethyl 4 and 2 g/day significantly decreased TG levels by 21.5% (P<0.0001) and 10.1% (P=0.0005), respectively. Secondary: Icosapent ethyl 4 and 2 g/day significantly decreased non-HDL-C by 13.6% (P<0.0001) and 5.5% (P=0.0054), respectively. Icosapent ethyl 4 g/day produced greater TG and non-HDL-C decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. Icosapent ethyl 4 g/day decreased LDL-C by 6.2% (P=0.0067) and decreased apo B (9.3%), TC (12.0%), VLDL-C

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
g/day (1 g twice daily) vs placebo twice daily (Icosapent ethyl is referred to by the investigational name AMR101 in this trial)		2 to 3 week qualifying period 12 weeks of treatment	change in non-HDL-C, LDL-C, apo B, VLDL, and lipoprotein-associated phospholipase A_2; safety	(24.4%), lipoprotein-associated phospholipase A_2 (19.0%), and hsCRP (22.0%) versus placebo (P<0.001 for all comparisons). Icosapent ethyl was generally well tolerated, with safety profiles similar to placebo.
Bhatt et al.[39] (2019) REDUCE-IT Icosapent ethyl 2 grams twice daily vs placebo	DB, MC, PC, RCT Patients with a fasting TG of 135 to 499 mg/dL and a LDL-C of 41 to 100 mg/dL who had been receiving a stable dose of a statin for at least 4 weeks and who were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional cardiovascular risk factor	N=8,179 Median of 4.9 years	Primary: Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina Secondary: Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	Primary: A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (HR, 0.75; 95% CI, 0.68 to 0.83; P<0.001). The absolute between-group difference was 4.8 percentage points (95% CI, 3.1 to 6.5). The number needed to treat to avoid one primary endpoint event was 21 (95% CI, 15 to 33) over a median follow-up of 4.9 years. Secondary: A key secondary efficacy end-point event occurred in 11.2% of the patients in the icosapent ethyl group, as compared with 14.8% of the patients in the placebo group (HR, 0.74; 95% CI, 0.65 to 0.83; P<0.001), corresponding to an absolute between-group difference of 3.6 percentage points (95% CI, 2.1 to 5.0); the number needed to treat to avoid one key secondary end-point event was 28 (95% CI, 20 to 47) over a median follow-up 4.9 years.
Bhatt et al.[40] (2020) REDUCE-IT	DB, MC, PC, RCT Patients in the U.S. with a fasting TG of	N=3,146 Median of 4.9 years	Primary: Composite of cardiovascular death, nonfatal	Primary: A primary endpoint occurred in 18.2% of patients treated with icosapent ethyl and in 24.7% of patients treated with placebo (HR, 0.69; 95% CI, 0.59 to 0.80; P=0.000001). The number needed to treat to avoid one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Icosapent ethyl 2 grams twice daily vs placebo	135 to 499 mg/dL and a LDL-C of 41 to 100 mg/dL who had been receiving a stable dose of a statin for at least 4 weeks and who were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional cardiovascular risk factor		myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina Secondary: Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	primary endpoint event was 15 over a median follow-up of 4.9 years. Secondary: A key secondary efficacy end-point event occurred in 12.2% of patients treated with icosapent ethyl and in 16.6% of patients treated with placebo (HR, 0.69; 95% CI, 0.57 to 0.83; P=0.00008). The number needed to treat to avoid one secondary endpoint event was 22 over a median follow-up of 4.9 years.
Bhatt et al.[41] (2019) REDUCE-IT Icosapent ethyl 2 grams twice daily vs placebo	DB, MC, PC, RCT Patients in the U.S. with a fasting TG of 135 to 499 mg/dL and a LDL-C of 41 to 100 mg/dL who had been receiving a stable dose of a statin for at least 4 weeks and who were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional cardiovascular risk	N=8,179 Median of 4.9 years	Primary: Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina Secondary: Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	Primary: Across 8,179 randomized patients, there were 1,606 (55.2%) first primary endpoint events and 1,303 (44.8%) subsequent primary endpoint events, for a total of 2,909 endpoint events. Overall, total (first and subsequent) primary endpoint event rates were 61 per 1,000 patient-years for patients treated with icosapent ethyl and 89 per 1,000 patient-years for patients treated with placebo (rate ratio, 0.70; 95% CI, 0.62 to 0.78; P<0.0001). Icosapent ethyl reduced totals for each component of the primary composite endpoint. Secondary: Overall, total key secondary endpoint event rates were 32 per 1,000 patient-years for patients treated with icosapent ethyl and 44 per 1,000 patient-years for patients treated with placebo (rate ratio, 0.72; 95% CI 0.63 to 0.82; P<0.0001).

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Peterson et al.[42] (2021) REDUCE-IT Icosapent ethyl 2 grams twice daily vs placebo	DB, MC, PC, RCT Patients in the U.S. with a fasting TG of 135 to 499 mg/dL and a LDL-C of 41 to 100 mg/dL who had been receiving a stable dose of a statin for at least 4 weeks and who were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional cardiovascular risk factor	N=8,179 Median of 4.9 years	Primary: Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina Secondary: Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	Primary: Across 8,179 patients, there were 920 (76.4%) first-event coronary revascularizations and 284 (23.6%) subsequent revascularization events for a total of 1,204 events. First coronary revascularization events were 9.2% (22.5 per 1,000 patient-years) for patients treated with icosapent ethyl and 13.3% (33.7 per 1,000 patient-years) with placebo (HR, 0.66; 95% CI, 0.58 to 0.76; P<0.000). The number needed to treat to avoid one first coronary revascularization event was 24 over a median follow-up of 4.9 years. Total revascularization events were reduced among patients taking icosapent ethyl versus placebo (rate ratio, 0.64; 95% CI, 0.56 to 0.74; P<0.0001). Icosapent ethyl significantly reduced percutaneous coronary intervention (HR, 0.68; 95% CI, 0.59 to 0.79; P<0.0001) and coronary artery bypass grafting (HR, 0.61; 95% CI, 0.45 to 0.81; P=0.0005). There were statistically significant RR reductions of ≥32% in time to first occurrences of elective, urgent, or emergent revascularizations as individual or composite end points.
Raal et al.[43] (2020) ORION-9 Inclisiran sodium (at a dose of 300 mg, which corresponds to a dose of 284 mg of inclisiran free acid) vs placebo	DB, MC, PC, RCT Adult patients with heterozygous familial hypercholesterolemia who had been treated with a maximally accepted dose of statin therapy with or without ezetimibe. Patients who were receiving a PCSK9 monoclonal antibody were excluded.	N=482 540 days	Primary: Percent change from baseline in the LDL-C level at day 510 and the time-adjusted percent change from baseline in the LDL-C level between day 90 and day 540 Secondary: Mean absolute change from	Primary: The percent change in the LDL-C level from baseline to day 510 was a decrease of 39.7% (95% CI, −43.7 to −35.7) in the inclisiran group and an increase of 8.2% (95% CI, 4.3 to 12.2) in the placebo group, for a between-group difference of −47.9 percentage points (95% CI, −53.5 to −42.3; P<0.001). For the second primary end point, the time-averaged percent change in the LDL-C level between day 90 and day 540 was a decrease of 38.1% (95% CI, −41.1 to −35.1) in the inclisiran group and an increase of 6.2% (95% CI, 3.3 to 9.2) in the placebo group, for a between group difference of −44.3 percentage points (95% CI, −48.5 to −40.1; P<0.001). Secondary: The mean absolute change from baseline in the LDL-C level at day 510 was a decrease of 59.0 mg per deciliter (95% CI, −64.8 to −53.2 [1.5

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both administered as a 1.5-ml subcutaneous injection on days 1, 90, 270, and 450			baseline in the LDL-C level at day 510, the time-adjusted absolute reduction from baseline between day 90 and day 540, and changes in levels of PCSK9, total cholesterol, apolipoprotein B, and non–HDL cholesterol	mmol per liter; 95% CI, −1.7 to −1.4]) in the inclisiran group and an increase of 9.9 mg per deciliter (95% CI, 4.1 to 15.8 [0.3 mmol per liter; 95% CI, 0.1 to 0.4]) in the placebo group, for a between-group difference of −68.9 mg per deciliter (95% CI, −77.1 to −60.7 [1.8 mmol per liter; 95% CI, −2.0 to −1.6]; P<0.001). The time-averaged observed difference in LDL cholesterol levels between day 90 and day 540 was −56.9 mg per deciliter (−1.5 mmol per liter) in the inclisiran group and 5.8 mg per deciliter (0.1 mmol per liter) in the placebo group, for a between-group difference of −62.6 mg per deciliter (−1.6 mmol per liter) (P<0.001), a difference of 44.6%. At day 510, the percent change in the PCSK9 level was a decrease of 60.7% (95% CI, −64.4 to −57.0) in the inclisiran group and an increase of 17.7% (95% CI, 13.9 to 21.4) in the placebo group, for a between-group difference of −78.4 percentage points (95% CI, −83.7 to −73.0; P<0.001). Inclisiran was associated with lower levels of total cholesterol, non–HDL cholesterol, apolipoprotein B, and triglycerides than placebo, along with higher HDL cholesterol levels.
Ray et al.[44] (2020) Inclisiran 284 mg vs placebo both administered as a 1.5-ml subcutaneous injection on days 1, 90, 270, and 450	DB, PC, PG, RCTs ORION-10: Patients with atherosclerotic cardiovascular disease who had elevated LDL-C levels despite receiving statin therapy at the maximum tolerated dose (United States) ORION-11: Patients with atherosclerotic cardiovascular disease or an	ORION-10: N=1561 ORION-11: N=1617 18 months	Primary: Percent change from baseline in the LDL-C level at day 510 and the time-adjusted percent change from baseline in the LDL-C level between day 90 and day 540 Secondary: Mean absolute change from baseline in the LDL-C level at day 510, the time-adjusted absolute	Primary: In the ORION-10 trial, the percentage change in LDL-C level at day 510 was 1.0% in the placebo group and −51.3% in the inclisiran group, resulting in a between-group difference of −52.3% (95% CI, −55.7 to −48.8; P<0.001). The time-adjusted change in LDL-C level after day 90 and up to day 540 (coprimary end point) as compared with baseline was 2.5% with placebo and −51.3% with inclisiran, representing a between-group difference of −53.8% (95% CI, −56.2 to −51.3; P<0.001). In the ORION-11 trial, the corresponding percentage change in LDL cholesterol level at day 510 was 4.0% in the placebo group and −45.8% in the inclisiran group, resulting in a between-group difference of −49.9% (95% CI, −53.1 to −46.6; P<0.001). The corresponding time-adjusted change in LDL cholesterol level was 3.4% with placebo and −45.8% with inclisiran, representing a between-group difference of −49.2% (95% CI, −51.6 to −46.8; P<0.001). Secondary: In the ORION-10 trial, the absolute change in LDL-C level at day 510 was −2.1 mg per deciliter (−0.05 mmol per liter) in the placebo group and

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	atherosclerotic cardiovascular disease risk equivalent who had elevated LDL-C levels despite receiving statin therapy at the maximum tolerated dose (Europe and South Africa)		reduction from baseline between day 90 and day 540, and changes in levels of PCSK9, total cholesterol, apolipoprotein B, and non–HDL cholesterol	−56.2 mg per deciliter (−1.45 mmol per liter) in the inclisiran group, with a between-group difference of −54.1 mg per deciliter (−1.40 mmol per liter) (95% CI, −57.4 to −50.9 mg per deciliter [−1.48 to −1.32 mmol per liter]; P<0.001). The time-adjusted absolute change in LDL-C level from day 90 to day 540 was −0.4 mg per deciliter (−0.01 mmol per liter) in the placebo group and −53.7 mg per deciliter (−1.39 mmol per liter) in the inclisiran group, with a difference of −53.3 mg per deciliter (−1.38 mmol per liter) (95% CI, −55.8 to −50.8 mg per deciliter [−1.44 to −1.31 mmol per liter]; P<0.001). In the ORION-11 trial, the corresponding absolute change in LDL-C level at day 510 was 1.0 mg per deciliter (0.03 mmol per liter) in the placebo group and −50.9 mg per deciliter (−1.32 mmol per liter) in the inclisiran group, with a between-group difference of −51.9 mg per deciliter (−1.34 mmol per liter) (95% CI, −55.0 to −48.7 mg per deciliter [−1.42 to −1.26 mmol per liter]; P<0.001). The time-adjusted absolute change in LDL-C level from day 90 to day 540 was 0.3 mg per deciliter (0.01 mmol per liter) in the placebo group and −48.6 mg per deciliter (−1.26 mmol per liter) in the inclisiran group, with a difference of −48.9 mg per deciliter (−1.26 mmol per liter) (95% CI, −51.4 to −46.5 mg per deciliter [−1.33 to −1.20 mmol per liter]; P<0.001). In the ORION-10 trial, the percentage change at day 510 was 13.5% with placebo and −69.8% with inclisiran, representing a between-group difference of −83.3% (95% CI, −89.3 to −77.3; P<0.001). Similarly, in the ORION-11 trial, the percentage change at day 510 was 15.6% with placebo and −63.6% with inclisiran, representing a between-group difference of −79.3% (95% CI, −82.0 to −76.6; P<0.001). In each trial, inclisiran resulted in improvement in other key secondary end points at day 510 as compared with placebo, including lower levels of total cholesterol, non-HDL cholesterol, and apolipoprotein B (P<0.001 for all three comparisons).
Samaha et al.[45] (2008) Group 1: ezetimibe 10 daily plus	DB, MC, RCT Hypercholesterolem-ic patients 18 to 70 years of age; Patients	N=85 12 weeks	Primary: Percentage change in LDL-C from baseline	Primary: Patients assigned to the combination of ezetimibe plus lomitapide experienced dose-dependent reductions in LDL ranging from 35 to 46% (P<0.001 vs ezetimibe alone). Patients assigned ezetimibe monotherapy experienced a 20 to 22% decrease in LDL-C levels after 12 weeks of

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placebo for 12 weeks vs group 2: lomitapide 5 mg for the first 4 weeks, 7.5 mg for the second 4 weeks, and 10 mg for the last 4 weeks, plus placebo for 12 weeks vs group 3: lomitapide (with the same dosing schedule as group 2) plus 10 mg ezetimibe daily for 12 weeks (Lomitapide is referred to by the investigational name AEGR-733 in this trial)	with 0 or 1 risk factors were required to have an LDL-C concentration between 160 and 250 mg/dL, and those with more than two risk factors were required to have an LDL-C concentration between 130 and 250 mg/dL		Secondary: Percentage changes in other serum lipoproteins (TC, non-HDL, VLDL, TG, HDL-C, Lp(a), apoB and apoA-I), change in body weight and overall safety and tolerability	therapy. Patients assigned to lomitapide monotherapy experienced dose-dependent reductions in LDL-C concentrations ranging from 19 to 30% (P=0.013 for a greater LDL reduction with 10 mg lomitapide alone vs 10 mg ezetimibe alone). Secondary: Patients receiving lomitapide monotherapy experienced dose-dependent decreases in concentrations of TC (23% at 10 mg), non-HDL-C (27% at 10 mg) and apoB (24% at 10 mg); these reductions were all greater than those observed with ezetimibe monotherapy. Further reductions in TC, non-HD-C, and apoB levels were observed in the group receiving combination therapy. TG did not change significantly from baseline in any of the three groups. Patients receiving lomitapide either alone or in combination with ezetimibe experienced a significant decrease in Lp(a) compared with those receiving ezetimibe alone. After 12 weeks, patients assigned ezetimibe monotherapy experienced a mean weight loss of 0.2 ±1.9 kg (0.1%); those assigned lomitapide monotherapy experienced a mean weight loss of 0.7 ±2.0 kg (1.0%); and those assigned combined lomitapide plus ezetimibe experienced a mean weight loss of 1.4 ±2.6 kg (1.4%); only the latter change was significant (P=0.013). However, the weight loss was not significantly different in the combination group vs the group receiving ezetimibe alone. Of the 85 patients enrolled, 18 (20%) either stopped or were taken off study medication before completion of the study, mainly owing to mildly elevated transaminase levels. This adverse event occurred in 9 of 56 (18%) patients who took lomitapide, either alone or in combination with ezetimibe, compared with none of the 29 patients assigned to ezetimibe alone. Transaminase levels returned to baseline in all these patients over the course of the protocol-specified, 2-week follow-up.
Cuchel et al.[46] (2013) Lomitapide at a starting dose of 5 mg/day for the first	OL, single-arm Patients ≥18 years of age with HoFH	N=29 78 weeks	Primary: Mean percent change in levels of LDL-C from baseline to week 26	Primary: Mean LDL-C significantly decreased by 50% from baseline to the end of the efficacy phase (week 26). Secondary: Mean TC, LDL-C, VLDL-C, non-HDL-C, TG, and apo B all decreased

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2 weeks and then escalated to 10, 20, 40, and 60 mg a day at 4-week intervals or until an individually determined maximum dose was achieved Patients continued current lipid-lowering therapy			Secondary: Percent changes in other lipid parameters, long-term safety (78 weeks), and changes in hepatic-fat content	between 45 and 50% from baseline (P<0.0001). Lp(a), HDL-C, and ApoA-I all also saw significant reductions at week 26. HDL-C, Lp(a), and ApoA-I returned to levels similar to those at baseline by week 78. The most commonly reported events during treatment with lomitapide were gastrointestinal (27 patients during the efficacy phase, and 17 during the safety phase). The three patients who discontinued the study because of gastrointestinal disorders permanently stopped lomitapide by week 12. No serious adverse events were reported between weeks 26 and 78. Ten patients had elevated levels of ALT, AST, or both of more than three times the upper limit of normal at least once during the study. Hepatic fat was measured non-invasively with nuclear magnetic resonance spectroscopy (NMRS). Mean hepatic fat in the 20 patients with evaluable NMRS scans was 1.0% (range 0 to 5.0) at baseline, 8.6% (0 to 33.6) at week 26, 5.8% (0 to 16.5%) at week 56, and 8.3% (0 to 19.0%) at week 78.
Stefanutti et al.[47] (2015) Lomitapide at a starting dose of 5 mg/day for the first two weeks and then escalated to 10, 20, 40, and 60 mg a day at 4-week intervals or until an individually determined maximum dose was achieved Patients continued current lipid-lowering therapy	Post-hoc analysis of Cuchel et al. Patients ≥18 years of age with HoFH, stratified by those who did or did not receive lipoprotein apheresis	N=29 78 weeks	Primary: Mean percent change in levels of LDL-C from baseline to week 26 Secondary: Percent changes in other lipid parameters	Primary: Of the 29 patients who entered the efficacy phase, 18 (62%) were receiving either lipoprotein apheresis or therapeutic plasma exchange at baseline. By the end of the efficacy phase (Week 26), during which apheresis schedules were to remain consistent, lomitapide was associated with a similar mean percent reduction in LDL-C from baseline irrespective of whether patients received apheresis or not. According to a mixed model repeated measures, overall percent reductions in LDL-C from baseline were −51.0% in all patients, −48.0% in those on apheresis and −55.1% in those not on apheresis (P=0.545). Secondary: Similarly, percent reductions in non-HDL-C (−48.3 vs −54.2%; P=0.613), TC (−43.8 vs −49.8%; P=0.575) and apoB (−47.9 vs −53.2%; P=0.625) were not significantly different between those on apheresis and those not. Changes in Lp(a) levels were modest and not different between groups (P=0.436).
Underberg et al.[48]	MC, OL, OS, PRO	N=187	Primary:	Primary:

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(2020) Lomitapide at median dose of 10 mg per day (range, 2.5 mg to 40 mg per day)	Patients initiating therapy with lomitapide or who have initiated therapy within three years before their enrollment in the Lomitapide Observational Worldwide Evaluation Registry (LOWER)	(N=173 patients with HoFH) Median of 1.98 years	Change from baseline in serum LDL-C Secondary: TC, non-HDL-C, apo B, TG, Lp(a), apo A1, VLDL-C, HDL-C	There was a mean 33% reduction in LDL-C in patients who initiated lomitapide and a 45% reduction in LDL-C in patients who initiated and remained on lomitapide. At any time after initiating lomitapide treatment, 58.4% of the patients experienced a reduction in LDL-C of at least 50% from baseline, 65.4% patients achieved LDL-C <100 mg/dL, and 41.1% patients achieved LDL-C <70 mg/dL. Secondary: When compared to baseline values at different timepoints (6 months, 1-, 2, 3-, 4-, and 5 years), the percent reduction in TC ranged from 21.3 to 30.4%, the percent reduction in non-HDL-C ranged from 4.8 to 36.4%, the percent change in HDL-C ranged from -14.1% to +7.2%, the percent change in VLDL-C ranged from -81.4 to +6.9%, and the percent change in TG ranged from -27.3 to +20.7%.
Elam et al.[49] (2000) Niacin IR (Niacor®) 3,000 mg per day or maximum tolerated dosage vs placebo	MC, PC, RCT Patients with peripheral arterial disease with or without diabetes, mean age 67 years for patients with diabetes and 65 years for those without diabetes	N=468 (N=125 patients with diabetes) Up to 60 weeks (12-week active run-in and 48-week double-blind)	Primary: Change in lipid profile, glucose, HbA_{1c}, ALT, uric acid; hypoglycemic drug use, compliance, adverse events Secondary: Not reported	Primary: Niacin use significantly increased HDL-C by 29 and 29% and decreased TG by 23 and 28% and LDL-C by 8 and 9%, respectively, in participants with and without diabetes compared to baseline (P<0.001 for niacin vs placebo for all). Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL; P=0.04 and P<0.001) in participants with and without diabetes, respectively. HbA_{1c} levels were unchanged from baseline to follow-up in participants with diabetes treated with niacin. In participants with diabetes treated with placebo, HbA_{1c} decreased by 0.3% (P=0.04 for difference). There were no significant differences in niacin discontinuation, niacin dosage, or hypoglycemic therapy in participants with diabetes assigned to niacin vs placebo. Secondary: Not reported
Capuzzi et al.[50] (1998)	ES, MC, OL Patients ≥18 years	N=517 Up to 96	Primary: Changes in LDL-C and apo B	Primary: Patients receiving niacin experienced significant reductions in LDL-C by 18% at week 48 and 20% at week 96. Similar reductions were seen with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Niacin ER (Niaspan®) titrated to 1 to 3 g per day Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction.	with primary hypercholesterolemia who were previously enrolled in a randomized short-term study or in a placebo-only qualification clinical trial	weeks	Secondary: Changes in TC, HDL-C, TC:HDL-C, Lp(a) and TG; adverse events	apo B (16% at week 48 and 19% at week 96). The percent changes achieved by both 48 and 96 weeks of therapy were statistically significant (P<0.001). Secondary: HDL-C significantly increased by 26% at week 48 and 28% at week 96 in patients receiving niacin. TC modestly decreased (12 and 13%, respectively), whereas the TC:HDL-C ratio decreased by almost one third (P<0.001 for all). TG and Lp(a) levels were decreased by 27 and 30%, respectively, at week 48, and by 28 and 40%, respectively, at week 96 (P<0.001 for all). Niacin was generally well tolerated. Flushing was common (75%); however, there was a progressive decrease in flushing with time from 3.3 episodes in the first month to ≤1 episode by week 48. Aspirin was used by one third of patients before niacin dosing to minimize flushing episodes. Six percent of patients discontinued therapy due to flushing. Serious adverse events occurred in about 10% of patients; however, none were considered probably or definitely related to niacin. No deaths or myopathy occurred. There were statistically significant increases in alkaline phosphatase, ALT, amylase, AST, direct bilirubin, glucose, and uric acid and a decrease in phosphorus (P<0.001 for all). Mean platelet counts decreased by 10.1% at week 48 and 14.8% at week 96, whereas leukocyte counts increased by 6.5% and 6.8%, respectively, at week 48 and week 96 of therapy (P<0.0001 for all).
Guyton et al.[51] (1998) Niacin ER (Niaspan®) titrated to 1 to 3 g per day Concomitant therapy with a statin,	ES, MC, OL Patients with primary hyperlipidemia who were previously enrolled in an RCT or in a placebo-only qualification clinical trial	N=269 patients treated up to 96 weeks and a cohort of N=230 patients treated for 3	Primary: Changes in TC, LDL-C, HCL-C, TG, apo B and Lp(a); safety Secondary: Not reported	Primary: The dosages of niacin attained by 269 patients were 1,000 mg (95% of patients), 1,500 mg (86%) and 2,000 mg (65%). After 96 weeks of treatment, niacin alone (median dose 2,000 mg) significantly reduced LDL-C (18%), TC (10%), and TG (26%), and increased HDL-C (32%). Apo B and Lp(a) were significantly reduced by 26 and 36%, respectively, at 48 weeks but values for these parameters were not available at 96 weeks (P<0.01 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction.		months (safety data)		At 96 weeks of the study, niacin plus a statin significantly lowered LDL-C (32%), TC (24%), and TG (32%) and increased HDL-C (25%) (P<0.01 for all values). Apo B (26%; P<0.01) and Lp(a) (19%; P value not significant) were also reduced at 48 weeks but values for these parameters were not available at 96 weeks. Niacin plus a bile acid sequestrant lowered LDL-C (28%) and TC (15%) and increased HDL-C (31%) (P<0.01 for all values). Niacin plus a bile acid sequestrant increased TG (5%; P value not significant). Apo B and Lp(a) were significantly reduced by 19 and 24% (P<0.01), respectively, at 48 weeks but values for these parameters were not available at 96 weeks. Intolerance to flushing led 4.8% of participants (13 of 269) to discontinue niacin. (Combining all of the data, 7.3% of patients discontinued niacin due to flushing.) Other medication-related adverse events leading to discontinuation from the 96-week study included nausea (3.3% of patients) sometimes with vomiting, other gastrointestinal symptoms (1.5%) and pruritus (2.6%). One case each of acanthosis nigricans, elevated glucose, gout, headache, palpitations and shoulder pain led to patient withdrawal. Overall, 9 of 499 (2.6%) patients experienced an ALT or AST elevation >2 times upper limit of normal. Five of these patients were on combination therapy, including four with a statin and one with a bile acid sequestrant. In five of the nine cases, the transaminase elevation resolved while niacin was continued without reduction in dose. Three cases led to niacin dosage reduction. One patient discontinued niacin because of transaminase elevations. Leg aches and myalgias with normal creatine kinase levels were described in one patient taking niacin with simvastatin. Secondary: Not reported
Gray et al.[52] (1994) Niacin SR	RETRO Male veterans with dyslipoproteinemia	N=969 1 to 36 months	Primary: Changes in lipid profile, alterations in hepatic enzymes	Primary: Lipoprotein responses were dose-related and favorable. Results included the following: TC -19.1%, LDL-C -24.0%, HDL-C 5.7%, and TG -32.5% (P≤0.0035 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Slo-Niacin®) average maintenance dose of 1.67 g per day	who were treated with niacin		and blood chemistry tests, hepatotoxicity Secondary: Not reported	Statistically but not clinically meaningful dose-related increases were seen in levels of liver enzymes and serum glucose (AST 29%, ALT 23%, alkaline phosphatase 25%, and glucose 7%; P=0.0001). Niacin was discontinued in 48.5% (435 of 896) of patients primarily because of adverse effects. The primary documented reasons for discontinuation included flushing and itching (8.9%), increased serum glucose (4.8%), gastrointestinal complaints (3.7%) and increased liver function tests (3.7%). Poor glycemic controlled to discontinuation in 40.6% (43 of 106) patients with diabetes mellitus. Twenty of 896 (2.2%) and 42 of 896 (4.7%) patients met biochemical criteria for "probable" and for "possible or probable" niacin-induced hepatotoxicity, respectively. Predisposing factors included high dose, alcohol use, preexisting liver disease and concurrent oral sulfonylurea therapy. Secondary: Not reported
Grundy et al.[53] (2002) Niacin ER (Niaspan®) 1,000 mg per day vs niacin ER (Niaspan®) 1,500 mg per day vs placebo	DB, PC, RCT Patients with stable type 2 diabetes, 47% were receiving concomitant statin therapy	N=148 16 weeks	Primary: Change in HDL-C, TG, HbA_{1c} Secondary: TC, LDL-C, FBG, adverse effects	Primary: Dose-dependent increases in HDL-C (13 to 19% for the 1,000 mg dose and 22 to 24% for the 1,500 mg dose; both P<0.05 vs placebo) and reductions in TG levels (-15 to -20% for the 1,000 mg dose; P value not significant, and -28 to -36% for the 1,500 mg dose; P<0.05) were observed. Changes in HbA_{1c} levels from baseline to week 16 were no different for niacin 1,000 mg/day (7.28 and 7.35%; P=0.16) and placebo (7.13 and 7.11%) but were significantly different for niacin 1,500 mg/day (7.2 and 7.5%; P=0.048). Secondary: Mean LDL-C levels were not significantly different than baseline for the placebo and niacin 1,000 mg groups. In the niacin 1,500 mg group, LDL-C levels decreased at all time points and the difference vs placebo was statistically significant at weeks 12 and 16 (P<0.05). The mean changes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				from baseline at 16 weeks were 9, 5 and -7% in the placebo, niacin 1,000 mg and 1,500 mg groups, respectively. Similar trends were observed for TC with mean increases of 4% in both the placebo and niacin 1,000 mg groups and a decrease of -6% in the niacin ER 1,500 mg group. In both the niacin groups, an initial rise in FBG was observed between weeks 4 and 8 which returned to baseline by week 16. Four patients in the niacin group (3 patients were receiving 1,500 mg) discontinued participation because of inadequate glucose control. Rates of adverse events other than flushing were similar for the niacin and placebo groups. Flushing was reported by about 67% of patients receiving niacin ER and about 10% of patients receiving placebo. Four patients, including 1 patient in the placebo arm, withdrew from the study due to flushing. No hepatotoxic effects or myopathy was observed.
Kuvin et al.[54] (2006) Niacin ER (Niaspan®) initially 500 mg at bedtime for 2 weeks then 1,000 mg at bedtime vs placebo	PC, RCT Patients with stable CAD and LDL-C <100 mg/dL, all received concurrent statin therapy (>80% atorvastatin)	N=60 3 months	Primary: Changes in lipoproteins, HDL and LDL particle distribution and inflammatory markers Secondary: Not reported	Primary: Six patients did not complete the protocol, two discontinued treatment due to flushing, and four were lost to follow-up. Niacin significantly increased total HDL-C by 7.5% and decreased TG by 15% compared to baseline (P<0.005 for both), whereas TC and LDL-C remained unchanged. Compared to baseline values, the addition of niacin resulted in a 32% increase in large-particle HDL (P<0.001) and an 8% decrease in small-particle HDL (P=0.0032). Addition of niacin produced an 82% increase in large-particle LDL (P=0.09) and a 12% decrease in small-particle LDL (P=0.008). Niacin also favorably altered inflammatory markers with lipoprotein-associated phospholipase A2 and CRP levels decreasing by 20 and 15%, respectively, compared to baseline (P<0.05 for both). No significant changes from baseline were seen in any tested parameter in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients who received placebo. No major cardiovascular events were reported during the study in the treatment or placebo group. Secondary: Not reported
Knopp et al.[55] (1998) Niacin IR titrated to 3 g per day vs niacin ER (Niaspan®) titrated to 1.5 g per day vs placebo	DB, MC, PG, RCT Patients with hypercholesterolemia, average age 54 years	N=223 25 weeks (9 week lead-in period)	Primary: Change in LDL-C, FPG, uric acid, drug tolerance Secondary: Change in TC, TG, HDL-C, HDL sub-fractions, apo B, apo AI, apo E, and Lp(a)	Primary: LDL-C was significantly reduced by 12, 12 and 22%, respectively, by niacin ER 1.5 g at bedtime, niacin IR 1.5 g/day, and niacin IR 3.0 g/day, respectively, compared to placebo (P≤0.05). At equal doses of 1.5 g/day of niacin ER vs niacin IR, AST increased 5.0% vs 4.8% (P value not significant), FPG increased 4.8 vs 4.5% (P value not reported), and uric acid concentration increased 6 vs 16% (P=0.0001), respectively. Flushing events were more frequent with niacin IR vs niacin ER (1,905 vs 575; P<0.001). Flushing severity was slightly greater with SR niacin, but still well tolerated. Secondary: Compared to placebo at eight weeks, niacin SR 1.5 g at bedtime vs niacin IR 1.5 g/day showed comparable efficacy in lowering TC, TG, apo B, apo E and Lp(a), and raising HDL-C, HDL2-C, HDL3-C and apo AI (P≤0.05 in all instances). Niacin IR 3.0 g/day produced significantly greater changes in the above lipid parameters compared to niacin IR 1.5 g/day and niacin ER 1.5 g at bedtime (P≤0.05).
McKenney et al.[56] (1994) Niacin IR BID, for a total daily dose of 500, 1,000, 1,500, 2,000 and 3,000 mg	DB, PG, RCT Patients with LDL-C >160 mg/dL after 1 month on a NCEP ATP III-Step 1 diet	N=46 36 weeks	Primary: Changes in LCL-C, HDL-C and TG; adverse events Secondary: Not reported	Primary: Niacin ER significantly decreased LDL-C more than niacin IR with doses of ≥1,500 mg/day (P<0.04 or P<0.001). Niacin IR significantly increased HDL-C more than niacin ER with all doses (P<0.04 or P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 6 weeks each vs niacin ER BID, for a total daily dose of 500, 1,000, 1,500, 2,000 and 3,000 mg for 6 weeks each				The reductions in TG levels were similar between niacin IR and ER with all doses, except for niacin IR 1,000 mg/day which led to significantly greater reductions (P=0.009). Nine of 23 patients (39%) receiving niacin IR withdrew before completing the 3,000 mg/day dose. Four patients withdrew at 1,000 mg/day, one at 1,500 mg/day, three at 2,000 mg/day and one at 3,000 mg/day. The most common reasons for withdrawal were vasodilatory symptoms, fatigue and acanthosis nigricans. Eighteen of 23 patients (78%) receiving niacin ER withdrew before completing the 3,000 mg/day dose. Two patients withdrew at 1,000 mg/day, two at 1,500 mg/day, seven at 2,000 mg/day and seven at 3,000 mg/day. The most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue and increases in liver function tests, often with symptoms of hepatic dysfunction. None of the patients receiving niacin IR developed hepatotoxic effects, while 12 patients (52%) receiving niacin ER did. Secondary: Not reported
Superko et al.[57] (2004) Niacin IR 3,000 mg/day vs niacin ER (Niaspan®) 1,500 mg/day vs placebo	PC, RCT Patients with hyper-cholesterolemia	N=218 14 weeks	Primary: Changes in lipid profile and Lp subclass distribution Secondary: Not reported	Primary: Niacin IR and ER significantly decreased TG, LDL-C, apo B and Lp(a), and significantly increased HDL-C (P≤0.0001 for all). Niacin IR and ER significantly increased mean LDL peak particle diameter and percent distribution of large LDL I and IIa, with a significant decrease in small LDL IIIa, IIIb, and IVb (P<0.05 for all, except for LDL I; P=0.12 for niacin ER). In general, the effects were greater in patients with LDL pattern B (predominance of dense LDL) compared to those with LDL pattern A (predominance of buoyant LDL). Compared to niacin IR, niacin ER 3,000 mg/day produced a smaller decrease in TG (-27 vs -47%; P<0.001), but had similar changes in LDL-C

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Results of 38 patients receiving niacin ER 3,000 mg/day from a previous trial were utilized in this analysis.				(-20 vs -22%; P value not reported), apo B (-22 vs -21%; P value not reported), HDL-C (27 vs 28%; P value not reported) and LDL peak particle diameter (0.90 vs 0.76 mm; P value not reported). Secondary: Not reported
Wi et al.[58] (2010) Niacin ER 500 mg/day for 5 weeks, followed by 1,000 mg/day for 4 weeks, followed by 1,500 mg/day vs fenofibrate 160 mg/day After discontinuation of any lipid modifying drug, patients entered an 8 week dietary run in period.	OL, RCT Patients 20 to 79 years of age with TG 150 to 499 mg/dL and HDL-C <45 mg/dL	N=201 24 weeks (includes 8 week dietary run in period)	Primary: Percent change from randomization to week 16 in apo B/apo AI Secondary: Percent changes in other lipid parameters, levels of glucose metabolism-related parameters, hsCRP	Primary: Apo B/apo AI was reduced with both treatments with no difference between the two (P=0.47). The percent reduction in apo B was greater with niacin, whereas the percent elevation in apo AI was higher with fenofibrate. Secondary: TC significantly decreased with both treatments, and TG decreased and HDL-C increased. LDL-C increased with fenofibrate but decreased with niacin. The percent reduction in TC was greater with niacin (P=0.01). TG decreased significantly more with fenofibrate (P=0.045), whereas the percent elevation in HDL-C was not different between the two treatments (P=0.22). The percent change in LDL-C was significantly different with the two treatments (P<0.001). Lp(a) levels were reduced with niacin only, and the change was significantly different compared to fenofibrate (P<0.001). FPG levels decreased with fenofibrate and increased significantly with niacin. HbA_{1c} levels increased with both treatments; the increase was borderline with fenofibrate and significant with niacin. The percent changes in FPG (P<0.001) and HbA_{1c} (P<0.001) levels were significantly different between the two treatments. Fasting insulin levels showed a borderline reduction with fenofibrate and a significant increase with niacin. HOMA-IR was decreased with fenofibrate and was increased with niacin. Percent changes of insulin (P<0.001) and HOMA-IR (P<0.001) were significantly different between the two treatments. hsCRP levels were significantly lowered with both treatments, but the percent change was greater with niacin (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Balasubramanyam et al.[59] (2011) Usual care vs low saturated fat diet and exercise (D/E) vs D/E and fenofibrate 145 mg/day (Tricor®) vs D/E and niacin SR 2,000 mg/day (Niaspan®) vs D/E and fenofibrate 145 mg/day and niacin SR 2,000 mg/day	DB, PC, RCT Patients 21 to 65 years of age with hypertriglyceridemia (fasting TG >150 mg/dL) and receiving stable ART therapy for 6 months	N=191 24 weeks	Primary: Baseline changes in lipid parameters Secondary: Baseline changes in insulin sensitivity, glycemia, adiponectin, CRP, energy expenditure, and body composition	Primary: Patients receiving fenofibrate achieved significant improvements in TG (P=0.002), TC (P=0.02), and non-HDL-C (P=0.003), compared to patients receiving niacin who achieved significant improvements in HDL-C (P=0.03), and both groups of patients achieved significant improvements in TC:HDL-C (P=0.005 and P=0.01). The combination of D/E plus fenofibrate plus niacin provided maximal benefit, reducing TG (-52% vs usual care; P=0.003), increasing HDL-C (12% vs usual care; P<0.001), and decreasing non-HDL-C (-18.5% vs usual care; P=0.003) and TC:HDL-C (-24.5% vs usual care; P<0.001). Secondary: Of the secondary endpoints evaluated, there was an effect of niacin on FPG (P=0.0002), oral glucose tolerance test area under the curve for glucose (P=0.02), fasting insulin (P=0.03), HOMA-IR (P=0.008), insulin sensitivity index (P=0.007), and adiponectin (P<0.0001), and an effect of fenofibrate on creatinine (P=0.002).
Guyton et al.[60] (2000) Niacin ER (Niaspan®) titrated up to 1,000 mg at bedtime for 4 weeks,	DB, MC, PC, RCT Patients 21 to 75 years of age with HDL-C ≤40 mg/dL, LDL-C ≤160 mg/dL or <130 mg/dL with	N=173 8 weeks	Primary: Effect on HDL-C Secondary: Change in other lipoproteins, adverse effects	Primary: Niacin 1,500 and 2,000 mg/day significantly increased HDL-C by 21 and 26%, respectively, compared to 13% with gemfibrozil (P<0.02). Secondary: Compared to gemfibrozil, niacin 1,500 and 2,000 mg/day significantly increased apo AI (9 and 11 vs 4%), reduced TC:HDL-C ratio (-17 and -22

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 1,500 mg at bedtime for 4 weeks, followed by 2,000 mg at bedtime for 8 weeks vs gemfibrozil 600 mg BID	atherosclerotic disease and TG ≤400 mg/dL			vs -12%), reduced Lp(a) (-7 and -20 vs no change) and had no adverse effect on LDL-C (2 and 0 vs 9%; P<0.001 to P<0.02.). TG decreased by 40% with gemfibrozil compared to 16 and 29% with niacin 1,000 (P<0.001) and 2,000 mg/day (P<0.06). Effects on plasma fibrinogen levels were significantly favorable for niacin compared to gemfibrozil (-1 to -6% vs 5 to 9%, respectively; P<0.02). Flushing was significantly more frequent with niacin compared to gemfibrozil at every point (78 vs 10%; P values not reported). Flu syndrome occurred more frequently with niacin (P=0.006). Dyspepsia was more frequent with gemfibrozil (P=0.009).
Alrasadi et al.[61] (2008) <u>Protocol 1</u> Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID for 8 weeks <u>Protocol 2</u> Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks vs	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	N=19 32 weeks	Primary: Percent changes in HDL-C and TC:HDL-C Secondary: Not reported	Primary: <u>Protocol 1</u> The mean percent change in HDL-C was +6, -6, and +22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +19, -26, and -22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). <u>Protocol 2</u> The mean percent change in HDL-C was -2 and +18% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC:HDL-C was +32 and -32% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC:HDL-C (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
niacin SR 1 g BID and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study in Protocol 2.				
Shearer et al.[62] (2012) Extended-release niacin (ERN, Niaspan 2g/day) vs P-OM3 (Lovaza, 4g/day) vs combination ERN and P-OM3 vs dual placebo All patients took aspirin 81 mg prior to dinner	DB, PC, RCT Patients age 40 to 69 years; BMI 25 to 40 kg/m^2; fasting TG, 150 to 750 mg/dL; HDL-C >10 mg/dL; and the ratio of TG/HDL-C >3.5	N=60 6-week, diet-stabilization, dual-placebo, run-in phase 16 weeks of treatment	Primary: Least squares mean changes, adjusted for baseline in non-HDL-C, HDL-C, TG, augmentation index, and reactive hyperemia index Secondary: Changes in TG:HDL, TC, LDL-C, VLDL-C, and lipoprotein subfractions	Primary: Significant improvements occurred in non-HDL-C, HDL-C, TG, and augmentation index with ERN treatment; TG with P-OM3 treatment; and HDL-C and TG with combination treatment. The TG reduction with combination treatment was greater than P-OM3 alone but was not greater than ERN (P=0.09). Secondary: No significant change from baseline in any group was observed for TC and LDL-C. Combination treatment had the greatest impact on lipoprotein subfractions, where improvements in particle density were observed. ERN significantly reduced the AI, a marker of vascular stiffness, by 3.5 units. No effect on this measure was observed in either P-OM3 or combination treatments. No significant effect of either agent (singly or combined) was observed on endothelial function measured by reactive hyperemia index or on blood pressure.
Guyton et al.[63]	DB, MC, RCT	N=1,220	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Niacin ER 2 g (titrated) per day and ezetimibe-simvastatin 10-20 mg QD vs niacin ER 2 g (titrated) per day vs ezetimibe-simvastatin (E/S) 10-20 mg QD	Patients 18 to 79 years of age with type IIa and IIb hyperlipidemia (LDL-C 130 to 190 mg/dL and TG ≤500 mg/dL)	24 weeks	Percent change from baseline in LDL-C, non-HDL-C, HDL-C, TG, TC, apo B, apo AI, and hsCRP Secondary: Not reported	After 24 weeks of therapy, the percent change from baseline in LDL-C, non-HDL-C, TG, apoB, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C were greater with niacin + E/S compared to treatment with niacin or E/S (P<0.001 for all). The percent change in HDL-C from baseline was significantly greater with niacin plus E/S compared to E/S (P<0.001). There was no significant difference with niacin plus E/S and niacin monotherapy (P>0.05). The percent change in TC from baseline was significantly greater with niacin plus E/S compared to niacin (P<0.001). There was no significant difference with niacin plus E/S and E/S monotherapy. The percent change in apoAI from baseline was significantly greater with niacin + E/S compared E/S (P<0.001). There was no significant difference with niacin + E/S and niacin monotherapy (P>0.05). Treatment with niacin + E/S led to a greater reduction in hsCRP compared to niacin monotherapy (P<0.005). Adverse events occurred more frequently in patients treated with niacin monotherapy and niacin + E/S compared to E/S monotherapy. This difference was due to flushing-related AEs in the niacin groups. Secondary: Not reported
Zhao et al.[64] (2004) Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose) vs	ES Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) including 25 with diabetes mellitus with mean LDL-C 128	N=160 38 months	Primary: Side effects, response to the question “Overall, how difficult is it to take the study medication?” Secondary: Not reported	Primary: Patients receiving niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo; any degree of flushing (30 vs 23%; P value not significant), symptoms of fatigue, nausea and/or muscle aches (9 vs 5%; P value not significant), AST at least three times the upper limit of normal (3 vs 1%; P value not significant), CPK at least two times the upper limit of normal (3 vs 4%; P value not significant), new onset of uric acid ≥7.5 mg/dL (18 vs 15%; P value not significant) and homocysteine ≥15 µmol/L (9 vs 4%; P value not significant).

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antioxidants (vitamin E 800 IU/day, vitamin C 1,000 mg/day, beta carotene 25 mg/day and selenium 100 µg/day) vs niacin plus simvastatin plus antioxidants vs placebo Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.	mg/dL, HDL-C 31mg/dL and TG 217 mg/dL			There were no side effects attributable to the antioxidant regimen. Glycemic control among diabetics declined mildly with niacin plus simvastatin, but returned to pre-treatment levels at month eight and remained stable for the rest of the trial. Niacin plus simvastatin was repeatedly described by 91% of treated patients vs 86% of placebo subjects as "very easy" or "fairly easy" to take. Secondary: Not reported
McKenney et al.[65] (2007) COMPELL Rosuvastatin 10 mg/day for 4 weeks, followed by 20 mg/day for 4 weeks, followed by 40 mg/day	MC, OL, PG, RCT Patients ≥21 years of age with hyper-cholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other	N=292 12 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects	Primary: Atorvastatin plus niacin SR, rosuvastatin plus niacin SR, simvastatin plus ezetimibe and rosuvastatin were associated with similar reductions in LDL-C (56, 51, 57 and 53%, respectively; P=0.093). Secondary: Atorvastatin plus niacin SR was associated with a significant increase in HDL-C compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (22, 10 and 7%, respectively; P≤0.05). There was no significant differences in the reduction of non-HDL-C from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atorvastatin 20 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by atorvastatin 20 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day vs simvastatin 20 mg/day plus ezetimibe 10 mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10 mg/day vs rosuvastatin 10 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by rosuvastatin 10 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by rosuvastatin 20 mg/day plus niacin	and mean TG ≤300 mg/dL			baseline with any treatment (P=0.053). Atorvastatin plus niacin SR was associated with a significant reduction in TG compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (47, 33 and 25%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in Lp(a) compared to simvastatin plus ezetimibe and rosuvastatin (20 mg)-containing therapy (-14, 7 and 18%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in apo B compared to rosuvastatin (43 vs 39%, respectively; P≤0.05). Side effects were similar across treatments (P values not reported). There were no cases of myopathy or hepatotoxicity reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SR 1,000 mg/day				
Fazio et al.[66] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day vs ezetimibe-simvastatin 10-20 mg/day At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.	DB, MC, RCT Patients 18 to 79 years of age with hyperlipidemia (Types IIa and IIb) with LDL-C 130 to 190 mg/dL, TG ≤500 mg/dL, creatinine <2 mg/dL, creatine kinase ≤2 times the upper limit of normal, transaminases ≤1.5 times the upper limit of normal and HbA_{1c} ≤8%	N=942 64 weeks	Primary: Safety and tolerability of ezetimibe/ simvastatin plus niacin ER Secondary: Changes in HDL-C, TG, non-HDL-C and LDL-C	Primary: The most frequent reason for discontinuation was clinical adverse events related to niacin-associated flushing with ezetimibe/simvastatin plus niacin (0.7% for ezetimibe/simvastatin vs 10.3% for ezetimibe/simvastatin plus niacin). A significant number of patients receiving ezetimibe/simvastatin plus niacin discontinued because of low LDL-C levels <50 mg/dL (1.5 vs 7.1%). The overall incidence of clinical adverse events was slightly greater for ezetimibe/simvastatin plus niacin compared to ezetimibe/simvastatin owing to the greater number of patients who experienced drug-related clinical adverse events and drug-related discontinuations with ezetimibe/simvastatin plus niacin, mainly attributed to niacin-associated flushing and pruritis. The percentage of patients with consecutive elevations in ALT or AST of at least three times or greater the upper limit of normal, and creatine kinase of at least ten times or greater the upper limit of normal were low and comparable between treatments. A total of 19 patients had adverse events of increased FPG levels, with eight receiving ezetimibe/simvastatin and 11 receiving ezetimibe/simvastatin plus niacin. Secondary: Ezetimibe/simvastatin plus niacin significantly improved baseline HDL-C, TG, non-HDL-C, LDL-C, apo B, apo AI and Lp ratios compared to ezetimibe/simvastatin at week 64 (P<0.004). The changes in TC were comparable between the two treatment groups and the reduction in hsCRP was numerically greater with ezetimibe/simvastatin plus niacin (P value not reported). Ezetimibe/simvastatin plus niacin increased HDL-C considerably during the first 16 weeks of treatment, and at a lower, but significant, rate from 16 to 24 weeks, and then remained constant throughout 64 weeks. The HDL-C change was significantly greater with ezetimibe/simvastatin plus niacin vs ezetimibe/simvastatin throughout the 64 weeks (P<0.001). The reductions in LDL-C, non-HDL-C and TG

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				observed after four weeks with ezetimibe/simvastatin plus niacin were maintained throughout the 64 weeks. In contrast, the levels remained relatively stable with ezetimibe/simvastatin throughout the 64 weeks (P<0.001) and became significant for non-HDL-C after eight weeks (P=0.002) and LDL-C after 12 weeks (P<0.001).
Fazio et al.[67] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day vs ezetimibe-simvastatin 10-20 mg/day At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.	Subgroup analysis Hyperlipidemic patients with diabetes mellitus, metabolic syndrome without diabetes mellitus or neither	N=765 at 24 weeks N=574 at 64 weeks	Primary: Changes in HDL-C, TG, non-HDL-C, LDL-C, fasting glucose and uric acid Secondary: Not reported	Primary: The effect of triple therapy on efficacy variables across patient subgroups was generally consistent with the significantly greater improvements observed in the total population compared to niacin and combination therapy. Triple therapy improved levels of LDL-C, other lipids and Lp ratios compared to niacin and combination therapy at 24 and 64 weeks. Triple therapy also increased HDL-C and Lp(a) comparably to niacin and more than combination therapy. Triple therapy also decreased hsCRP more effectively than niacin and comparably to combination therapy. Fasting glucose trended higher for niacin compared to combination therapy. Glucose elevations from baseline to 12 weeks were highest for patients with diabetes (niacin, 24.9 mg/dL; triple therapy, 21.2 mg/dL and combination therapy, 17.5 mg/dL). Fasting glucose levels then declined to pretreatment levels at 64 weeks in all subgroups. New onset diabetes was more frequent among patients with metabolic syndrome than those without for the first 24 weeks and trended higher among those receiving niacin (niacin, 5.1%; combination therapy, 1.7% and triple therapy, 8.8%). Between weeks 24 and 64, five and one additional patient(s) receiving combination (cumulative incidence, 5.9%) and triple therapy (cumulative incidence, 9.2%) were diagnosed with diabetes. Treatment-incident increases in uric acid were higher among patients receiving niacin, but there were no effects on symptomatic gout. Secondary: Not reported
Pownall et al.[68] (1999)	DB, PC, PG, RCT Patients with severe	N=40 12 weeks	Primary: Effect on TG, lipid profile, and lipid	Primary: Median TG levels were reduced 38.9% from baseline in the omega-3 acid ethyl ester group compared to 7.8% with placebo (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	hypertriglyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)		composition Secondary: Not reported	Omega-3 acid ethyl esters also significantly reduced TC (-9.9%; P=0.004) and VLDL-C (-29.2%; P=0.001) and significantly increased LDL-C (16.7%; P=0.007) from baseline. HDL-C increased in patients receiving omega-3 acid ethyl esters (5.9%; P=0.057 vs baseline and P=0.023 vs placebo) and decreased in patients receiving placebo (-5.9%; P value not significant vs baseline). Secondary: Not reported
McKeone et al.[69] (1997) Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, RCT Patients with severe hypertriglyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks	Primary: Effect on TG and serum phospha-tidylcholine Secondary: Changes in lipid profile	Primary: Treatment with omega-3 acid ethyl esters significantly reduced TG levels by 26% compared to a 7% increase for placebo. Incorporation of eicosapentaenoic and docosahexaenoic acid into the serum phosphatidylcholine occurred within 6 weeks and was usually accompanied by a reduction in plasma TG. Secondary: Omega-3 acid ethyl esters also significantly reduced VLDL-C (28%) and TC (11%), and increased HDL-C (14%). None of these parameters significantly changed in the placebo group.
Calabresi et al.[70] (2000) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks vs placebo for 8 weeks	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 26 weeks	Primary: Changes in lipid profile and LDL-C subclass distribution Secondary: Safety	Primary: Omega-3 acid ethyl esters significantly lowered plasma TG and VLDL-C by 27 and 18%, respectively (both P<0.05) compared to baseline. TC and HDL-C did not change but LDL-C and apo B increased by 21% (P=0.05) and 6% compared to baseline (P<0.05). Omega-3 acid ethyl esters treatment caused a redistribution of LDL-C subclasses towards less dense lipoprotein particles (possibly indicative of a less atherogenic LDL-C profile); however, the average LDL-C size did not change. Secondary: Omega-3 acid ethyl esters were well tolerated with no reports of drug-related adverse events or negative safety parameters (e.g., glucose, uric acid, liver enzymes, kidney function, and platelet count).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Calabresi et al.[71] (2004) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks vs placebo for 8 weeks	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 20 weeks	Primary: Changes in lipid profile, LDL-C and HDL-C subclass distribution Secondary: Not reported	Primary: Plasma TG were 44% lower and LDL-C and apo B were 25 and 7% higher after omega-3 acid ethyl esters than placebo (P<0.05 for all). HDL-C was higher (8%) after omega-3 acid ethyl esters than placebo but this difference did not reach statistical significance (P>0.05). Omega-3 acid ethyl esters caused a selective increase of the more buoyant HDL_2-C subfraction; plasma HDL_2-C and total mass increased by 40% (P<0.05) and 26%, respectively, whereas HDL_3-C and total mass decreased by 4% (P>0.05) and 6%. The plasma concentration of the HDL-bound antioxidant enzyme paraoxonase increased by 10% after omega-3 acid ethyl esters (P<0.05). Secondary: Not reported
Bays et al.[72] (2010) Omega-3 acid ethyl ester (Lovaza®) 4 g/day vs placebo All patients received atorvastatin 10 mg/day for 8 weeks, 20 mg for 4 weeks, and 40 mg for 4 weeks.	DB, MC, PC, RCT Patients 18 to 79 years of age with hypercholesterolemia (non-HDL-C >160 mg/dL and TG 250 to 599 mg/dL)	N=245 16 weeks	Primary: Percent change in non-HDL-C level between baseline and week eight Secondary: Percent changes in non-HDL-C level between baseline and the end of treatment with atorvastatin at 20 mg and 40 mg, percent changes in TC, HDL-C, LDL-C, VLDL-C, TG, apo AI and apo B concentrations	Primary: After eight weeks of therapy, the median percent change in non-HDL-C was -40.2% in the omega-3 acid ethyl ester group and -33.7% in the placebo group (90% CI, -7.2 to -2.9; P<0.001). Secondary: Omega-3 acid ethyl ester significantly reduced non-HDL-C compared to placebo during the atorvastatin 20 mg phase (-7.9%; 90% CI, -9.1 to -4.9; P<0.001) and atorvastatin 40 mg phase (-4.1%, 90% Cl, -6.8 to -2.4; P<0.001). There was no significant difference in the percentage of patients who achieved LDL-C goals with omega-3 acid ethyl ester (85.7%) or placebo groups (91.5%; P=0.20). There was no significant difference in the percentage of patients who achieved non-HDL-C goals with omega-3 acid ethyl ester (88.7%) or placebo groups (87.8%; P>0.99). Treatment with omega-3-acid ethyl esters with all doses of atorvastatin significantly reduced TC (P<0.001), TC:HDL-C (P<0.001), TG (P<0.001), VLDL-C (P<0.001), RLP-C (P<0.001) and increased HDL-C (P<0.001) compared to treatment with placebo with all doses of atorvastatin. There

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was no significant difference in LDL-C, apo AI, or apo B between the treatment groups. There was no significant difference in adverse events among the treatment groups.
Durrington et al.[73] (2001) <u>Phase I</u> Omega-3 acid ethyl esters (Omacor*) 2 g BID for 24 weeks vs placebo for 24 weeks All patients received simvastatin. <u>Phase II</u> Omega-3 acid ethyl esters (Omacor*) 2 g BID and simvastatin 10 to 40 mg QD for 24 weeks	DB, RCT Patients ≤75 years of age with established CHD who were already receiving treatment with simvastatin 10 to 40 mg daily and who had TG >203 mg/dl	N=59 48 weeks	Primary: Percent change in TG and VLDL-C, as well as effects on other lipid parameters Secondary: Not reported	Primary: Serum TG and VLDL-C significantly decreased with omega-3 acid ethyl esters compared to baseline or placebo (20 to 30% reduction; P<0.0005 and 30 to 40% reduction; P<0.005, respectively). There were no adverse effects on other lipid parameters with omega-3 acid ethyl esters, including LDL-C and HDL-C. There were no significant adverse events with omega-3 acid ethyl esters. Secondary: Not reported
Nordoy et al.[74] (1998) Omega-3 acid ethyl esters (Omacor*) 4 g per/day vs placebo	DB, PC, RCT Patients 25 to 60 years of age with combined hyperlipidemia receiving simvastatin 20 mg for 5 to 10 weeks	N=41 5 weeks	Primary: Lipid and lipoprotein parameters Secondary: Not reported	Primary: The addition of omega-3 acid ethyl esters to simvastatin therapy led to an increase in EPA (P<0.0002) and DHA (P<0.0003) and reduction in linoleic acid (P=0.001). The addition of omega-3 acid ethyl esters to simvastatin led to a reduction in TC (P=0.052) and TG (P<0.001). There was no significant effect on HDL-C with omega-3 acid ethyl esters. There was no effect on apo A1 or apo B with the addition of omega-3 acid

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received simvastatin 20 mg QD.				ethyl esters to simvastatin; however, there was a significant reduction in the concentration of apo E (P=0.035). Secondary: Not reported
Davidson et al.[75] (2007) Omega-3-acid ethyl ester (Lovaza®) 4 g/day vs placebo All patients were receiving simvastatin 40 mg/day.	DB, MC, PC, PG, RCT Adult patients who have received ≥8 weeks of stable statin therapy and have a mean fasting TG ≥200 and <500 mg/dL and mean LDL-C below or within 10% NCEP ATP III goal	N=254 16 weeks (includes 8 weeks OL treatment with simvastatin)	Primary: Change in non-HDL-C Secondary: Changes in TG, VLDL-C, LDL-C, HDL-C, TC and apo B; adverse events	Primary: At the end of treatment, the median percent change in non-HDL-C was significantly greater with omega-3-acid ethyl esters compared to placebo (-9.0 vs -2.2%; P<0.001). Secondary: Treatment with omega-3-acid ethyl esters was associated with significant reductions in TG (2.9 vs 6.3%), VLDL-C (27.5 vs 7.2%) and TC:HDL-C ratio (9.6 vs 0.7%), and a significant increase in HDL-C (3.4 vs -1.2%) (*P*<0.001 for all). Adverse events reported by at least one percent of patients treated with omega-3-acid ethyl esters that occurred with a higher frequency than those receiving simvastatin monotherapy were nasopharyngitis (3.3%), upper respiratory tract infection (3.3%), diarrhea (2.5%) and dyspepsia (2.5%). There was no significant difference in the frequency of adverse events between treatment groups. No serious adverse events were considered treatment related.
Maki et al.[76] (2010) COMBOS Omega-3-acid ethyl esters (Lovaza®) 4 g/day vs placebo All patients received simvastatin 40	DB, PC, RCT Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥8 weeks prior to trial enrollment	N=256 8 weeks	Primary: Non-HDL-C levels Secondary: TG, VLDL-C, LDL-C and HDL-C levels	Primary: Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest (<80.4 mg/dL), middle (80.4 to <99.0 mg/dL) and highest (≥99.0 mg/dL) tertiles achieved a percent change from baseline in non-HDL-C of the following: -5 vs 0%, -13 vs -4% and -11 vs -2% (P values not reported). Secondary: Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in TG of the following: -27 vs -8%, -32 vs -5% and -30 vs -6% (P values not reported). Use of omega-3-acid ethyl esters and placebo in patients with a baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day.				LDL-C in the lowest, middle and highest (≥99.0 mg/dL) tertiles achieved a percent change from baseline in VLDL-C of the following: -27 vs -7%, -28 vs -10% and -29 vs -7% (P values not reported). Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in LDL-C of the following: 9.5 vs 1.1%, -0.9 vs -3.8% and -6.4 vs -4.5% (P values not reported). The baseline LDL-C tertile had a significant interaction with treatment for the LDL-C response (P=0.022). Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in HDL-C of the following: 4 vs -1%, 2 vs -1% and 4 vs -1% (P values not reported).
Bays et al.[77] (2010) COMBOS Omega-3-acid ethyl esters (Lovaza®) 4 g/day plus simvastatin 40 mg/day Patients who received placebo in the COMBOS trial were switched to OL treatment with omega-3-acid ethyl esters plus simvastatin (Switchers). Those who received omega-3-acid ethyl	ES, OL of COMBOS Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥8 weeks prior to trial enrollment	N=188 Up to 24 months	Primary: The difference between Nonswitchers and Switchers in median percent change in non-HDL-C from COMBOS end of treatment to month four Secondary: Difference in the median percent change in non-HDL-C from COMBOS end of treatment to month 12 and 24; the change in non-HDL-C from	Primary: The percent change in non-HDL-C from COMBOS end of treatment to month four revealed a greater response among Switchers when compared to Nonswitchers. At month four, the median percent change in non-HDL-C from the end of DB treatment was -9.4% in Switchers and 0.9% in Nonswitchers (P<0.001). Secondary: After 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS end of treatment in Nonswitchers vs Switchers was -0.2 vs -0.64% (P=0.027) and 1.6 vs -6.3% (P=0.004). Reductions in non-HDL-C were maintained throughout the trial. After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in the total population was -8.3, -7.3 and -8.9%, respectively (P<0.001 for all). After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in Nonswitchers vs Switchers was -5.4 vs -10.3% (P=0.062), -6.6 vs -8.1% (P=0.604) and -7.8 vs -9.0% (P=0.496). Consistent with the non-HDL-C response, comparisons of the changes from the COMBOS end of treatment to months four, 12 and 24 in TG and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
esters plus simvastatin in the COMBOS trial were maintained on current therapy (Nonswitchers) All patients continued therapeutic lifestyle changes diet.			COMBOS baseline to months four, 12 and 24 and from COMBOS end of treatment to months four, 12 and 24; percent changes in TC, HDL-C, LDL-C, VLDL-C, TG and TC:HDL-C for the same time points; HbA_{1c} levels	other lipoprotein lipid parameters generally revealed greater reductions in Switchers vs Nonswitchers. The comparisons of the change from COMBOS baseline to these same endpoints reveled generally nonsignificant differences between the two groups. Median percent reductions from COMBOS baseline in TG, TC and VLDL-C in the total population were maintained at months four, 12 and 24 of treatment (P<0.001 for all). Omega-3-acid ethyl esters produced small median percent increases from baseline LDL-C levels at months four, 12 and 24. Among the subset of patients who had HbA_{1c} measured at baseline (n=38), the median absolute change in HbA_{1c} after 24 months of treatment was 0.1% (P value not reported).
Maki et al.[78] (2008) Omega-3 acid ethyl esters (Lovaza®) 4 g/day vs placebo All patients received simvastatin 20 mg/day.	RCT, XO Patients 18 to 79 years of age with mixed dyslipidemia (TG 200 to 600 mg/dL and non-HDL-C above NCEP ATP III goal)	N=40 12 weeks	Primary: Lipid and lipoprotein parameters Secondary: Not reported	Primary: Treatment with omega-3 acid ethyl esters resulted in a -40% reduction in non-HDL-C compared to -34% with placebo (P<0.001). Treatment with omega-3 acid ethyl esters resulted in significantly greater changes in other lipid parameters compared to placebo, including VLDL-C (-42 vs -22%, respectively), TG (-44 vs -29%, respectively), TC (-31 vs -26%, respectively), and HDL-C (-16 vs -11%, respectively; P<0.05 for all). There was no significant difference in LDL-C with omega-3 acid ethyl esters (-37%) and placebo (-38%; P=0.433). Treatment with omega-3 acid ethyl esters resulted in significantly greater changes in other lipoprotein parameters compared to placebo, including apo B (-32 vs -28%, respectively), TC:HDL-C ratio (-39 vs -33%, respectively), and TG:HDL-C ratio (-51 vs -37%, respectively). There was no significant difference in apo AI levels with omega-3 acid ethyl esters (0.9) and placebo (4.3%; P=0.667). Secondary: Not reported
Peters et al.[79] (2012) Omega-3 PUFA	DB, MC, PC, RCT HIV-infected adult patients receiving	N=48 12 weeks	Primary: Change in baseline mean fasting TG, biochemical and	Primary: Omega-3 PUFA reduced TG by a mean of 1.75 mmol/L vs a 0.41 mmol/L increase with placebo (baseline-corrected percentage change related to placebo 95% CI, -69.48 to -6.53; P=0.019).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients were allowed to receive fenofibrate or niacin.	HAART therapy and a fasting TG level 3.39 to 11.3 mmol/L		virologic safety parameters Secondary: Safety	No effect was observed on biochemical or virologic safety parameters. Secondary: No severe treatment-emergent adverse events occurred. Mild to moderate treatment-emergent adverse events were reported in 20 and 19 patients receiving omega-3 PUFA and placebo. Most treatment-emergent adverse events were gastrointestinal-related and included diarrhea, nausea, and flatulence.
Kim et al.[80] (2018) ROMANTIC Omega-3 fatty acids 4 grams/day with rosuvastatin 20 mg/day vs placebo with rosuvastatin 20 mg/day	DB, MC, PC, RCT Patients 19 to 80 years of age with fasting TG level ≥300 mg/dL and LDL-C level ≥100 mg/dL and <160 mg/dL for individuals who were not taking statins for 4 weeks, TG level ≥200 mg/dL and <500 mg/dL, and LDL-C level <110 mg/dL for individuals who were taking statins for last 4 weeks, and nonsmoking during the study period	N=201 8 weeks	Primary: Lipid and lipoprotein parameters Secondary: Adverse events	Primary: The percentage change at eight weeks from baseline in TG levels was significantly greater with the omega-3 group compared with the placebo group (−26.3 vs −11.4%, P<0.001). There was also a greater reduction of non–HDL-C levels in the omega-3 group than in the placebo group (−10.7 vs −2.2%, P=0.001). Among other lipid parameters, total cholesterol, VLDL-C, Apo A1, and Apo B also had a greater decrease in the omega-3 group than in the placebo group (P<0.05 for each). Meanwhile, LDL-C and HDL-C levels slightly increased in both groups, but the difference between the groups was not statistically significant (LDL-C: 1.8 vs 4.3%, P=0.335; HDL-C: 0.9 vs 2.8%, P=0.377). Secondary: There was no significant difference between groups in adverse events (15.5% in the omega-3 group vs 17.3% in the placebo group, P=0.732).
Roth et al.[81] (2009) <u>Phase I</u> Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3)	DB, MC, PC, RCT Patients 18 to 79 years of age with Fredrickson type IV dyslipidemia, BMI 25 to 43 kg/m^2, and TG 500 to 1,300	N=167 16 weeks	Primary: Median percent change in TG Secondary: Additional lipid and cardiovascular risk factors	Primary: After eight weeks of therapy, median TG values were reduced from 649.5 to 267.5 mg/dL (-60.8%) with P-OM3 + FENO and from 669.3 to 310 mg/dL (-53.8%) with FENO monotherapy (P=0.059). There was no significant difference between the treatment groups (P=0.059). Secondary: LDL-C was significantly increased with P-OM3 + FENO compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD for 8 weeks vs fenofibrate 130 mg (FENO) QD and placebo for 8 weeks <u>Phase II</u> Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks	mg/dL			FENO monotherapy (48.2 vs 39.0%, respectively; P=0.030). There was no significant difference in non-HDL-C among the treatment groups (-8.2% for P-OM3 + FENO vs -7.1% for FENO; P=0.767). There was a greater reduction in VLDL-C with P-OM3 + FENO than with FENO monotherapy (-57.6 vs -47.6%, respectively; P=0.016). There was a greater reduction in RLP-C with P-OM3 + FENO than with FENO monotherapy (-72.0 vs -62.1%; P=0.029). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly reduced TGs compared to the end of the DB treatment period (-17.5%; P=0.003). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly increased LDL-C (+8.1%; P=0.001) compared to the group previously receiving P-OM3 + FENO (+0.4%). There was no significant change in non-HDL-C following the addition of P-OM3 to FENO. VLDL-C and RLP-C were significantly reduced by the addition of P-OM3 (-15.4%; P=0.030 and -25.8%; P=0.035, respectively). There was no significant difference in final lipid results for those who received P-OM3 + FENO for 16 weeks and those in which P-OM3 was added to FENO monotherapy during the OL phase of the study. In the pooled analysis of all patients enrolled in the eight week OL extension phase, the overall reductions of TGs and VLDL-C were -60.0 and -56.5%, respectively (P<0.001 for both). Non-HDLC and TC were also significantly reduced (P<0.001) over the 16 week treatment period in the pooled analysis. LDL-C increased 52.2% (P<0.001). There was no significant change in apo B at the end of the 16 week treatment study (P=0.544). The treatments were generally well tolerated and there was no significant difference in the safety profiles. The most adverse events were upper respiratory infection, nausea, diarrhea, constipation, gastroenteritis,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				dyspepsia, and headache.
Koh et al.[82] (2012) Omega-3 fatty acids 2 g/day vs fenofibrate 160 mg/day vs placebo	PC, PG, RCT, SB Patients with primary hypertriglyceridemia (>150 mg/dL)	N=50 2 months	Primary: Change in baseline lipid profile; change in baseline vasomotor function, hsCRP, and fibrinogen; change in baseline adiponectin, HbA_{1c}, and insulin resistance Secondary: Not reported	Primary: Placebo treatment significant reduced TG and TG:HDL-C, but increased LDL-C from baseline. Omega-3 fatty acids significantly reduced TG and TG:HDL-C from baseline. Fenofibrate significantly reduced T C, TG, apo B, TG:HDL-C, and non-HDL-C, and increased HDL-C and apo AI from baseline. Effects of fenofibrate on TC and T G were both significant compared to placebo (P<0.05). The magnitude of change in HDL-C, apo AI, TG:HDL-C, and non-HDL-C were significantly different when omega-3 fatty acids and fenofibrate therapy were compared, but both treatments resulted in comparable improvements in TG (P<0.05). Placebo did not significantly improve flow-mediated dilator response to hyperemia, but omega-3 fatty acids and fenofibrate significantly improved flow-mediated dilator response to hyperemia after two months when compared to baseline (P<0.001), and when compared to placebo (P<0.001). Brachial artery dilator responses to nitroglycerin were not significantly different between any of the therapies. Placebo and omega-3 fatty acids did not significantly change hsCRP and fibrinogen levels relative to baseline measurements. Fenofibrate significantly reduced hsCRP and fibrinogen levels after two months compared to baseline (P<0.001) or when compared to placebo (P<0.05). Omega-3 fatty acids did not significantly change insulin, plasma adiponectin levels, or insulin sensitivity compared to placebo. Compared omega-3 fatty acids, fenofibrate significantly decreased fasting insulin (P=0.023) and increased plasma adiponectin (P=0.002) and insulin sensitivity (P=0.015). Secondary: Not reported
Stalenhoef et al.[83] (2000) Omega-3 acid ethyl esters (Omacor*) 4 g per day	DB, DD, RCT Patients with primary hyper-triglyceridemia	N=28 12 weeks	Primary: Change in lipid profile, LDL-C subfraction profile Secondary:	Primary: Both omega-3-acid ethyl esters and gemfibrozil resulted in similar and significant decreases in serum TG, VLDL-TG and VLDL-C concentrations and increases in HDL-C and LDL-C (P=0.05 to P<0.001 from baseline and P=0.29 to P=1.00 between groups).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs gemfibrozil 1,200 mg per day			Not reported	Both therapies resulted in a more buoyant LDL-C subfraction profile (P=0.05 for omega-3-acid ethyl esters, P<0.01 for gemfibrozil and P=0.09 between groups in favor of gemfibrozil). Secondary: Not reported
van Dam et al.[84] (2001) Omega-3 acid ethyl esters (Omacor*) 4 g/day vs gemfibrozil 1,200 mg/day	DB, RCT Patients with hypertriglyceridemia (TG >400 mg/dL)	N=89 12 weeks	Primary: Percent change in TG Secondary: Percent change in TC, HDL-C, VLDL-C	Primary: The mean percent change in TG was -28.9% with omega-3 acid ethyl esters and -51.2% with gemfibrozil (P=0.007). Secondary: The mean percent change in HDL-C and TC were 1.2 and -10.2%, respectively, with omega-3 acid ethyl esters and 27.9 and -13.0%, respectively, with gemfibrozil (P=0.012 and P=0.513, respectively). The mean percent change in VLDL-C was -11.8% with omega-3 acid ethyl esters and -19.4% with gemfibrozil (P=0.494).
Trials Assessing Cardiovascular Outcomes				
Nissen et al.[85] (2023) Bempedoic acid 180 mg QD vs placebo	DB, PC, RCT Patients 18 to 85 years of age with a previous cardiovascular event or clinical features that placed them at high risk for a cardiovascular event, reported being unable or unwilling to receive statins owing to an adverse effect that had started or increased during statin therapy and resolved or improved after statin therapy	N=13,970 40.6 months (median follow-up duration)	Primary: Four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization Secondary: Three-component composite of death from cardiovascular	Primary: A primary end-point event occurred in 819 patients (11.7%) in the bempedoic acid group and in 927 patients (13.3%) in the placebo group (HR, 0.87; 95% CI, 0.79 to 0.96; P=0.004). Secondary: Death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction occurred in 575 patients (8.2%) in the bempedoic acid group and in 663 patients (9.5%) in the placebo group (HR, 0.85; 95% CI, 0.76 to 0.96; P=0.006). Fatal or nonfatal myocardial infarction occurred in 261 patients (3.7%) in the bempedoic acid group and in 334 patients (4.8%) in the placebo group (HR, 0.77; 95% CI, 0.66 to 0.91; P=0.002). Coronary revascularization occurred in 435 patients (6.2%) in the bempedoic acid group and in 529 patients (7.6%) in the placebo group (HR, 0.81; 95% CI, 0.72 to 0.92; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	was discontinued		causes, nonfatal stroke, or nonfatal myocardial infarction; fatal or nonfatal myocardial infarction; coronary revascularization; fatal or nonfatal stroke; death from cardiovascular causes; and death from any cause	The results for the other key secondary end points (fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause) did not differ significantly between the bempedoic acid group and the placebo group.
Coronary Drug Project[86] (1975) Niacin IR 3,000 mg per day vs clofibrate 1.8 g per day vs placebo	DB, MC, PC, RCT Men 30 to 64 years of age with previous MI	N=8,341 5 years	Primary: All-cause mortality Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death), nonfatal cardiovascular events	Primary: The incidence of all-cause mortality was comparable between niacin (24.4%), clofibrate (25.5%) and placebo (25.4%) (P values not significant). Secondary: Five year rates of death due to cardiovascular disease were comparable between niacin (18.8%), clofibrate (17.3%) and placebo (18.9%) (P values not significant). Major cardiovascular events were reduced with niacin; CHD events by 13%, nonfatal MI by 27% and cerebrovascular events by 21%. Niacin significantly reduced the incidence of nonfatal MI compared to placebo (8.9 vs 12.2%; P<0.004). There was no evidence of significant efficacy of clofibrate with regard to all-cause and cause-specific mortality. Treatment with niacin for five years lowered TC by 10% and TG levels by 26% (P values not reported). Treatment with clofibrate lowered TC by 7% and TG levels by 22% (P values not reported).
Canner et al.[87] (1986)	ES of the Coronary Drug Project	N=8,341	Primary: All-cause mortality	Primary: A follow-up of patients nine years after completion of the Coronary Drug

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Coronary Drug Project Niacin IR 3,000 mg per day vs placebo	Men 30 to 64 years of age with previous MI	9 years	Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death)	Project trial (total mean follow up of 15 years) revealed that niacin reduced the risk of all-cause mortality by 11% (52.0 vs 58.2%; P=0.0004 vs placebo). Secondary: The survival benefit with niacin was primarily evident for death caused by CHD (36.5 vs 41.3%; P<0.05 vs placebo).
Lee et al.[88] (2009) Niacin ER (Niaspan®) 2,000 mg per day vs placebo	DB, PC, RCT Patients with pre-existing atherosclerosis and low HDL-C (<40 mg/dL) in whom LDL-C was treated with statins	N=71 1 year	Primary: Absolute change in carotid artery wall area and change in carotid plaque index Secondary: Not reported	Primary: Patients receiving niacin had a significantly greater change in carotid wall area at 12 months compared to placebo (difference -1.64 mm^2; 95% CI, -3.12 to -0.16; P=0.03). After 12 months of therapy, the change in carotid plaque index was significantly reduced by niacin compared to placebo (difference -0.016; 95% CI, -0.03 to -0.0022; P=0.02). Niacin increased HDL-C by 23% and decreased LDL-C by 19%. TG, apo B, and Lp(a) were significantly decreased by niacin compared to placebo. CRP was decreased by niacin compared to placebo (P=0.03 at six months and P=0.1 at 12 months). Adiponectin was significantly increased at both six and at 12 months (P<0.01). Secondary: Not reported
Taylor et al.[89] (2004) Niacin ER (Niaspan®) 1,000 mg/day vs	DB, PC, RCT Adult patients with known CHD and low levels of HDL-C (<45 mg/dL)	N=167 1 year	Primary: Change in mean common CIMT after one year Secondary: Changes in lipid concentrations,	Primary: After one year, mean CIMT increased significantly with placebo (0.044±0.100 mm; P<0.001) and was unchanged with niacin (0.014±0.104 mm; P=0.23). The overall difference in CIMT progression between placebo and niacin was not significant (P=0.08); however, a post hoc analysis revealed that niacin significantly reduced the rate of CIMT progression in subjects

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo All patients received background statin therapy.			composite of clinical cardiovascular events (including any hospitalization for an acute coronary syndrome, stroke, revascularization procedure or sudden cardiac death), adverse events	without insulin resistance (P=0.026). Secondary: HDL-C increased by 21% with niacin and did not change with placebo (P<0.003). Clinical cardiovascular events occurred in three patients receiving niacin (3.8%) and seven receiving placebo (9.6%; P=0.20). Adherence to trial medication based on pill counts ranged from 90.3 to 94.5%, and was not different between the two treatments (P value not reported). No patient experienced significant (three times the upper limit of normal) elevations of liver enzymes or developed myositis. At the end of the trial, skin flushing was reported in 69.2 and 12.7% of patients receiving niacin and placebo (P<0.001).
Philpott et al.[90] (2013) Niacin ER vs placebo	DB, PC, XO, RCT Patients with stable coronary disease on high dose statin therapy	N=66 24 weeks (12 weeks of each treatment)	Primary: Effect of niacin on flow-mediated dilation Secondary: Effect of niacin on the microvascular responses of pulse arterial tonometry and hyperemic velocity	Primary: There was no significant difference between Niacin ER and placebo on flow-mediated dilation. Secondary: Measures of microvascular function were not statistically different with niacin therapy.
AIM-HIGH Investigators[91] (2011) Niacin ER (Niaspan) 1500 to 2000 mg daily	MC, RCT Patients were 45 years of age or older and had established CV disease, low baseline levels of HDL-C (<40 mg/dL	N=3414 3 years	Primary: Composite of the first event of death from CHD, nonfatal MI, ischemic stroke, hospitalization (for >23 hours) for an	Primary: The primary end point occurred in 282 patients in the niacin group (16.4%) and 274 in the placebo group (16.2%) (HR with niacin, 1.02; 95% CI, 0.87 to 1.21; P=0.80 for the superiority of niacin therapy with the use of a Cox proportional-hazards model and P=0.79 by the log-rank test). Secondary: Niacin therapy had a similar lack of effect on the composite secondary end

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Both groups received daily simvastatin adjusted to LDL-C and ezetimibe 10 mg could also be added on All patients underwent a 4 to 8 week open-label phase of simvastatin 40 mg plus niacin titration from 500 mg to 2000 mg daily. Patients tolerating ≥1500 mg niacin were randomized	for men; <50 mg/dL for women), elevated TG (150 to 400 mg/dL), and LDL-C <180 mg/dL if not taking a statin at entry Patients who were screened were required to discontinue lipid-modifying drugs, except for statins or ezetimibe, at least 4 weeks before enrollment		acute coronary syndrome, or symptom-driven coronary or cerebral revascularization Secondary: Composite end points included death from CHD, nonfatal MI, ischemic stroke, or hospitalization for a "high-risk" acute coronary syndrome; death from CHD, nonfatal MI, or ischemic stroke; and death from CV causes	point of death from CHD, nonfatal MI, ischemic stroke, or hospitalization for a high-risk acute coronary syndrome (HR, 1.08; 95% CI, 0.87 to 1.34; P=0.49) and on the composite secondary end point of death from CHD, nonfatal MI, or ischemic stroke (HR, 1.13; 95% CI, 0.90 to 1.42; P=0.30). The number of patients who died from CV causes was low in both the niacin group and the placebo group (45 patients [2.6%] and 38 patients [2.2%], respectively; P=0.47).
Teo et al.[92] (2013) AIM-HIGH Niacin ER (Niaspan) 1500 to 2000 mg daily vs placebo Both groups received daily	MC, RCT Patients enrolled in the AIM-HIGH trial	N=3414 3 years	Primary: Ischemic stroke risk Secondary: Not reported	Primary: Of the 50 fatal or nonfatal ischemic strokes, there were an excess number of events in the statin–niacin combination group (HR, 1.78; 95% CI, 1.00 to 3.17; P=0.050). There were seven hemorrhagic strokes and 30 transient ischemic attacks (TIAs) among participants. The HR for the composite ischemic strokes and TIA was 1.20 (95% CI, 0.77 to1.88; P=0.428). Multivariate stepwise regressions analyses showed independent associations between ischemic stroke risk and ≥65 years of age (HR, 3.58; 95% CI, 1.82 to 7.05; P=0.0002), a history of stroke/TIA/carotid disease (HR, 2.18; 95% CI, 1.23 to 3.88; P=0.0079), and elevated baseline Lp(a) (HR, 2.80; 95% CI, 1.25 to 6.27 comparing the middle with the lowest tertile and HR, 2.31; 95% CI, 1.00 to 5.30 comparing the highest with the lowest tertile; overall P=0.042) but a nonsignificant association between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin adjusted to LDL-C and ezetimibe 10 mg could also be added on All patients underwent a 4 to 8 week open-label phase of simvastatin 40 mg plus niacin titration from 500 mg to 2000 mg daily. Patients tolerating ≥1500 mg niacin were randomized				ischemic stroke and combination therapy (HR, 1.74; 95% CI, 0.97 to 3.11; P=0.063). Secondary: Not reported
Phan et al.[93] (2014) FATS-OS Combination therapy (lovastatin 40 mg/day, niacin 2 to 3 g/day, and colestipol 20 gm/day for 11 years, then continued with simvastatin 10 to 80 mg/day or lovastatin 40 to 80 mg/day plus niacin 2 to 4 g/day vs conventional	Case-control study Patients enrolled in the Familial Atherosclerosis Treatment Study (FATS), which randomized 176 men with elevated apo B levels and CAD	N=69 20 years	Primary: Mean common CIMT Secondary: Association between lipids levels and mean common CIMT	Primary: The mean CIMT measured in the combination group was significantly smaller as compared with the usual care group (0.902 ± 0.164 vs 1.056 ± 0.169 mm, P<0.001). Secondary: After 20 years, there were significant changes in lipoprotein levels observed in both groups. The combination therapy group had a greater percent decrease in TC (−42 ± 14 vs −31 ± 17%; P=0.008) and LDL-C (−57 ± 13 vs −38 ± 25%; P<0.001), greater percent increase in HDL-C (38 ± 43 vs 15 ± 23%, P=0.02), and greater decrease in TG (−28 ± 44 vs −1.0 ± 49%, P=0.03) as compared with usual care. CIMT was correlated with combination therapy (−0.154; −0.24 to −0.07; P<0.001), on-therapy LDL-C (0.201; 0.069 to 0.332; P=0.003), and percent change in LDL-C (0.04; 0.005 to 0.091; P=0.03). As compared with the usual care group, the combination treated group had a significantly younger mean vascular age (74.4 ± 16.5 years vs 84.6 ± 13.5 years; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy (88% single statin therapy)				
Phan et al.[94] (2013) Treatment with niacin vs Treatment not including niacin	Combined analysis (4 RCTs) Patients with established vascular disease without a diagnosis of diabetes mellitus who had been treated with or without niacin and had a baseline fasting glucose level <100 mg/dL	N=407 3 years	Primary: Change in FPG, development of impaired fasting glucose. Frequency of new-onset diabetes, change in mean coronary stenosis and major CV events Secondary: Not reported	Primary: Patients treated with niacin had a significantly larger increase in glucose levels than those not taking niacin (9.88 vs 4.05 mg/dL, P=0.002). The glucose increase was not associated with the type or dosage of niacin used. Impaired fasting glucose was significantly more likely to be seen in subjects treated with niacin than in those without niacin treatment (38% [78 of 197] vs 21% [44 of 210], P=0.003). A non-significant greater number of incident diabetes was found in the niacin group (5.6% [11 of 197] vs 4.8% [10 of 210]; P=0.5). After three years of therapy, the niacin-treated patients had a mean change in the percentage of stenosis that was significantly less than that in the untreated subjects (0.1 ± 0.3% vs 2 ± 12%, P<0.0001). Of the niacin-treated patients, 8% had major CV events during follow-up, significantly less than the 21% of untreated patients experiencing major cardiac events (P=0.0001). Secondary: Not reported
Illingworth et al.[95] (1994) Lovastatin 10 to 80 mg/day vs niacin IR 0.25 mg to 1.5 g TID	MC, OL, RCT Patients 21 to 75 years of age with primary hyper-cholesterolemia and either an LDL-C >160 mg/dL and CHD or ≥2 CHD risk factors without CHD or LDL-C >190 mg/dL without CHD or ≥2 risk factors after rigorous diet	N=136 26 weeks	Primary: Change from baseline in lipid parameters Secondary: Safety	Primary: Lovastatin reduced TC, LDL-C and apo B significantly more than niacin (P<0.01 for all). At weeks 10, 18 and 26, LDL-C was reduced by 26, 28 and 32% with lovastatin compared to five, 16 and 21% with niacin, respectively. The target treatment goal of LDL-C <130 mg/day for patients with CHD or less than two risk factors was achieved in 14, 19 and 35% of patients receiving lovastatin compared to zero, 18 and 26% of patients receiving placebo at weeks 10, 18 and 26, respectively (P values not significant). For the majority of those patients with CHD or two or more risk factors in whom the LDL-C goal was <110 mg/dL, neither drug was effective in achieving this goal. In these patients only 13 and 11% achieved this goal at week 26, respectively (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Niacin was more effective in decreasing TG at week 26 (P<0.01 vs lovastatin). Both treatments were effective in reducing VLDL-C, with no significant difference observed between the two treatments (P value not reported). Niacin produced reductions in Lp(a) of 14, 30 and 35% at weeks 10, 18 and 26, whereas lovastatin had no effect (P<0.05 or P<0.01 between drugs at each time point). Niacin was significantly more effective at increasing HDL-C and apo AI (P<0.01 vs lovastatin), except for the change in apo AI at week 10 (P value not reported). Niacin increased HDL-C by 20, 29 and 33% and apo AI by 11, 19 and 22% at weeks 10, 18 and 26. Lovastatin resulted in a modest increase in HDL-C and apo AI of 7 and 6%, respectively, at week 26. Secondary: Four deaths occurred in the trial, one with niacin and three with lovastatin. All were related to atherosclerosis, and none were deemed to be drug-related. Five and nine patients receiving lovastatin and niacin discontinued treatment because of adverse experiences (excluding deaths). For those who discontinued treatment, the reason was considered to be drug-related in four and eight patients receiving lovastatin and niacin (P value not significant). The major reasons for discontinuation of niacin were cutaneous complaints, including flushing, pruritis and rash. One patient discontinued lovastatin because of myalgias. Overall, patient tolerance to the treatments was better with lovastatin. Adverse events (in decreasing frequency) that occurred more frequently with niacin include flushing, paresthesia, pruritis, dry skin, nausea/vomiting, asthenia and diarrhea.
Sang et al.[96] (2009)	RCT Patients with clinical	N=108 12 months	Primary: All-cause mortality, MI,	Primary: At 12 months, clinical events included rehospitalization due to angina pectoris and heart failure attack, respectively, revascularization with PCI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atorvastatin 10 mg/day vs atorvastatin 10 mg/day and niacin ER	and angiographic criteria for coronary disease, with ≥50% stenosis of 1 coronary artery with high TC	(plus a 12 month follow up)	rehospitalization, revascularization with either PCI or CABG Secondary: Mean percent changes from baseline lipid parameters, effects on glucose metabolism, safety	and sudden death (7.14%) with atorvastatin. With combination therapy, the clinical events included rehospitalization due to heart failure attack, revascularization after PCI or CABG (5.77%). No significant reduction was observed with combination therapy (OR, 0.78; P=0.052). Secondary: TC, TG, LDL-C and Lp(a) levels decreased significantly with both treatments (P<0.01), with no significant difference between the two during the course of follow up (P>0.05). Apo A increased significantly with both treatments (P<0.01), with a more favorable effect observed with combination therapy (24.5 vs 40.8%; P<0.01). During the follow up, apo B fell by 5.63 (P<0.05 and 7.35% (P<0.01) with atorvastatin and combination therapy; with no significant difference between the two (P>0.05). During the trial, HDL-C levels increased by 11.67 (P<0.05) and 29.36% (P<0.01) with atorvastatin and combination therapy, with a significant difference favoring combination therapy (P<0.01). Niacin resulted in no significant increase in glucose levels at six or 12 months compared to baseline levels (P>0.05). In the subgroup of diabetic patients (n=28), niacin resulted in a significant increase in glucose levels at six months (P<0.01), and glucose levels increased more significantly at 12 months (P<0.01), but the effect of niacin was not significant in nondiabetic patients (P>0.05). HbA_{1c} levels did not show a significant increase at six months in patient with diabetes, but levels increased significantly at 12 months (P<0.05). Both treatments were generally well tolerated. The most common side effect of niacin therapy was flushing which appeared in four patients receiving combination therapy; however, all patients continued the medication and the flushing disappeared.
Taylor et al.[97] (2009) Niacin ER (Niaspan®) 2 g (titrated) QD	OL, PG, RCT Patients ≥30 years of age with atherosclerotic coronary or vascular disease or a CHD risk	N=208 14 months	Primary: Change in CIMT after 14 months Secondary: Change in lipid values, composite	Primary: Treatment with niacin led to a significant reduction in mean and maximal CIMT at eight months (P=0.001 and P=0.004, respectively) and 14 months (P=0.001 and P<0.001, respectively). There was no significant change in mean or maximal CIMT with ezetimibe at eight or 14 months compared to baseline. There was a significant difference between the niacin group and the ezetimibe group (P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ezetimibe 10 mg QD	equivalent (diabetes mellitus, 10-year Framingham risk score ≥20%, coronary calcium score >200 for women or >400 for men who were receiving treatment with a statin (LDL-C <100 mg/dL and HDL-C <50 mg/dL for men or <55 mg/dL for women)		of major adverse cardiovascular events (MI, myocardial revascularization, admission to the hospital for an acute coronary syndrome, and death from CHD), discontinuation of study drug due to adverse effects, health-related quality of life	Secondary: The change in LDL-C in the ezetimibe group was -17.6 mg/dL compared to -10.0 mg/dL in the niacin group (P=0.01). The change in HDL-C in the ezetimibe group was -2.8 mg/dL compared to 7.5 mg/dL in the niacin group (P<0.001). There were significant reductions in TG in both groups. Major adverse cardiovascular events occurred in 5% of patients receiving ezetimibe compared to 1% of patients receiving niacin (P=0.04). Adverse drug effects led to withdrawal from the study in three of nine patients receiving ezetimibe and 17 of 27 patients receiving niacin (P=0.12). There was no significant difference between the two groups in the quality of life at baseline or at 14 months.
Brown et al.[98] (2001) HATS Niacin SR (Slo-Niacin®) titrated to 1 g BID and simvastatin vs antioxidants vs niacin SR (Slo-Niacin®) titrated to 1 g BID, simvastatin, and antioxidants	DB, PC Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) and with ≥3 stenoses of ≥30% of the luminal diameter or 1 stenosis of ≥50%, low HDL-C, normal LDL-C	N=160 3 years	Primary: Changes in lipid profile, arteriographic evidence of change in coronary stenosis (% stenosis caused by most severe lesion in each of nine proximal coronary segments), occurrence of first cardiovascular event (death from coronary causes, MI, stroke or revascularization) Secondary: Mean change in %	Primary: The mean levels of LDL-C, HDL-C, and TG were significantly changed by -42% (P<0.001), 26% (P<0.001) and -36% (P<0.001), respectively, in the niacin plus simvastatin group but were unaltered in the antioxidant only and placebo groups. Similar changes were observed when antioxidants were added to niacin plus simvastatin. The protective increase in HDL_2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (65%) was attenuated by concurrent therapy with antioxidants (28%; P=0.02). The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (P=0.16 compared to placebo) and 0.7% with niacin plus simvastatin plus antioxidants (P=0.004), and regressed by 0.4% with niacin plus simvastatin (P<0.001). The frequency of the composite primary end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebos, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary end point was 90% lower in the niacin plus simvastatin group than placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.			stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions and all lesions	(P=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group. Secondary: In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenoses and were supported by the results for the mean minimal luminal diameter.
Blankernhorn et al.[99] (1987) Colestipol 30 g/day plus niacin 3 to 12 g/day vs placebo	DB, PC, RCT Nonsmoking men 49 to 59 years of age with progressive atherosclerosis who had coronary bypass surgery not involving valve replacement performed ≥3 months prior and a fasting blood cholesterol level 185 to 350 mg/dL	N=188 2 years	Primary: Coronary global change score Secondary: Change from baseline in lipid parameters	Primary: Deterioration in overall coronary status was significantly less with combination therapy compared to placebo (P<0.001). Atherosclerosis regression, as indicated by perceptible improvement in overall coronary status, occurred in 16.2 and 2.4% of patients receiving combination therapy and placebo (P=0.002). Combination therapy resulted in a significant reduction in the average number of lesions per patient that progressed (P<0.03) and the percentage of patients with new atheroma formation in native coronary arteries (P<0.03). The percentage of patients receiving combination therapy with new lesions (P<0.04) or any adverse change in bypass grafts (P<0.03) was significant reduced. Secondary: Large, significant decreases in TC (26 vs 4%), TG (22 vs 5%), LDL-C (43 vs 5%) and LDL-C/HDL-C (57 vs 6%), and a large, significant increase in HDL-C (37 vs 2%) were achieved with combination therapy compared to placebo (P<0.001 for all). Modifications in lipid parameters achieved with combination therapy were significant compared to baseline values (P values not reported).
Brown et al.[100] (1990)	DB, RCT	N=120	Primary: Average change in	Primary: On average, placebo (conventional therapy) increased the index of stenosis

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Colestipol 5 to 10 g TID plus niacin 125 mg BID titrated to 1 to 1.5 g TID vs Colestipol 5 to 10 g TID plus lovastatin 20 mg BID titrated to 40 mg BID vs placebo (or colestipol if LDL-C was elevated)	Men ≤62 years of age with elevated apo B and a family history of CAD	32 months	the percent stenosis for the worst lesion in each of the nine proximal segments Secondary: Average changes in all lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	by 2.1 percentage points a baseline of 34%. By contrast, it decreased by 0.7 percentage points with colestipol plus lovastatin and by 0.9 percentage points with colestipol and niacin (P<0.003 for trend). At trial end, on average, these nine lesions were almost 3 percentage points less severe among patients treated intensively compared to conventionally. This difference represents almost 1/10 of the amount of disease present at baseline (34% stenosis). Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease when looking at the effect of treatment on certain subsets of lesions (all lesions measured in each patient, lesions causing severe or mild stenosis and those that did not cause total occlusion at baseline). The results with both treatment groups were significantly difference from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.
Eritsland et al.[101] (1996) Omega-3 acid ethyl esters (Omacor®*) 4 g/day vs dietary therapy	RCT Patients admitted for coronary artery bypass grafting without concomitant cardiac surgery	N=610 1 year	Primary: Graft occlusion Secondary: Not reported	Primary: After one year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving omega-3 acid ethyl esters compared to 33% in the control group (OR, 0.77, 95% CI, 0.60 to 0.99; P=0.034). In the omega-3 acid ethyl esters group, 43% of the patients had 21 vein grafts occluded compared to 51% of the patients in the control group (OR, 0.72, 95% CI, 0.51 to 1.01; P=0.05). Secondary: Not reported
Johansen et al.[102] (1999) Omega-3 acid ethyl esters (Omacor*) 3 g BID	DB, PC, RCT Patients who were scheduled for elective coronary angioplasty for one or more lesions in native	N=500 6 months	Primary: Restenosis Secondary: Not reported	Primary: Restenosis occurred in 40.6% of the treated stenoses in the omega-3 acid ethyl esters group and in 35.4% of the treated stenoses in the placebo group (OR, 1.25; 95% CI, 0.87 to 1.80; P=0.21). One or more restenoses occurred in 45.9% of patients treated with omega-3 acid ethyl esters compared to 44.8% of patients receiving placebo (OR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	coronary arteries who had not undergone prior angioplasty			1.05; 95% CI 0.69 to 1.59; P=0.82). Secondary: Not reported
Nilsen et al.[103] (2001) Omega-3 acid ethyl esters (Omacor*) 3 g BID vs placebo	PC, RCT Patients >18 years of age with acute MI	N=300 Up to 2 years	Primary: Cardiac events and revascularizations Secondary: Not reported	Primary: Of the patients receiving omega-3 acid ethyl esters, 28% experienced at least one cardiac event compared to 24% of patients in the placebo group (P=0.74). There was no significant difference between the groups with regards to the number, type, or severity of cardiac events. There was no significant difference in the number of revascularizations with omega-3 acid ethyl esters or placebo (HR, 0.92; 95% CI 0.61 to 1.38). Secondary: Not reported
GISSI-Prevenzione Investigators[104] (1999) Omega-3 acid ethyl esters 1 g/day vs vitamin E 300 mg/day vs omega-3 acid ethyl esters 1 g/day vitamin E 300 mg/day vs	MC, OL, RCT Patients surviving a recent (≤3 months) MI	N=11,324 3.5 years	Primary: Cumulative rate of all-cause death, nonfatal MI and nonfatal stroke; cumulative rate of cardiovascular death, nonfatal MI, nonfatal stroke Secondary: Analyses of components of primary end points and main causes of death, adverse events	Primary: Treatment with omega-3 PUFA, but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI and nonfatal stroke (RR, 10%; 95% CI, 1 to 18; P=0.048 by 2-way analysis and RR, 15%; 95% CI, 2 to 26; P=0.023 by 4-way analysis). Treatment with omega-3 PUFA decreased the risk of the composite of cardiovascular death, nonfatal MI and nonfatal stroke (RR, 11%; 95% CI, 1 to 20; P=0.053 by 2-way analysis and RR, 20%; 95% CI, 5 to 32; P=0.008 by 4-way analysis). The effect of the combined treatment with omega-3 PUFA and vitamin E was similar to that for omega-3 PUFA for the primary end point (RR, 14%; 95% CI, 1 to 26) and for fatal events (RR, 20%; 95% CI, 5 to 33). Secondary: Analyses of the individual components of the main end point showed that the decrease in mortality (20% for total deaths [P value not reported], 30% for cardiovascular deaths [P=0.0242] and 45% for sudden deaths [P=0.010]) which was obtained with omega-3 PUFA accounted for all of the benefit seen in the combined end point. There was no difference across

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no treatment				the treatment groups for nonfatal cardiovascular events. At one year and at the end of the trial, 11.6 and 28.5% of patients receiving omega-3 PUFA and 7.3 and 26.2% of those receiving vitamin E, respectively, had permanently stopped taking the study drug. Side effects were reported as a reason for discontinuing therapy for 3.8% of patients in the omega-3 PUFA groups and 2.1% of those in the vitamin E groups. Overall, gastrointestinal disturbances and nausea were the most frequently reported side effects (4.9 and 1.4% with omega-3 PUFA and 2.9 and 0.4% with vitamin E, respectively; P values not reported.).

*Omacor was renamed to Lovaza in August 2007.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate release, QD=once daily, SR=sustained release, TID=three times daily
Study abbreviations: DB=double-blind, ES=extension study, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, XO=crossover
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo=apolipoprotein, AST=aspartate aminotransferase, BMI=body mass index, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, CIMT=carotid intima-media thickness, CPK=creatinine phosphokinase, CRP=C-reactive protein, CV=cardiovascular, DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, FBG=fasting blood glucose, HAART=high active antiretroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HeFH=heterozygous familial hypercholesterolemia, HIV=human immunodeficiency virus, HoFH=homozygous familial hypercholesterolemia, HOMA-IR=homeostasis model assessment-insulin resistance, HR=hazard ratio, hsCRP=high sensitivity C reactive protein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, PCI=percutaneous coronary intervention, PUFA=polyunsaturated fatty acids, RLP-C=remnant like particle cholesterol, RR=relative risk, TC=total cholesterol, TG=triglycerides, VLDL-C=very low-density lipoprotein cholesterol

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 Antilipemic Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Bempedoic acid	tablet	Nexletol®	$$$$$	N/A
Bempedoic acid and Ezetimibe	tablet	Nexlizet®	$$$$$	N/A
Evinacumab-dgnb	injection	Evkeeza®	$$$$$	N/A
Icosapent ethyl	capsule	Vascepa®*	$$$$$	$$$$
Inclisiran	injection	Leqvio®	$$$$$	N/A
Lomitapide	capsule	Juxtapid®	$$$$$	N/A
Niacin	extended-release tablet*	Niaspan®*	$$$$	$
Omega-3 acid ethyl esters	capsule	Lovaza®*	$$$$$	$

*Product is available over-the-counter.
N/A=Not available.

X. Conclusions

Prescription niacin, icosapent ethyl, and omega-3 acid ethyl esters are approved by the Food and Drug Administration (FDA) for the treatment of hypertriglyceridemia.[4-6] Lomitapide and evinacumab are approved for adjunctive treatment of homozygous familial hypercholesterolemia (HoFH).[11,12] Bempedoic acid, bempedoic acid/ezetimibe, and inclisiran are approved for adjunctive treatment of heterozygous familial hypercholesterolemia (HeFH).[9,10,13] Prescription niacin is also approved for the treatment of primary

hypercholesterolemia and mixed dyslipidemia.[4] Niacin is available over-the-counter (OTC) in immediate-release and sustained-release formulations. Niacin is also available by prescription. Niacin extended release, icosapent ethyl, and omega-3 acid ethyl esters are available in a generic formulation.

In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant, or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels and are recommended in patients with established coronary heart disease (CHD) or CHD equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or ezetimibe should be considered.[18,20,24] More recent guidelines discourage use of niacin in combination with statins, as trials have shown increased side effects without any reduction in cardiovascular outcomes.[21] The FDA has withdrawn approval it had previously given for use of niacin with statins to treat high cholesterol, citing a lack of cardiovascular benefit.[4,105] In patients with an elevated triglyceride level (≥500 mg/dL) a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis. Omega-3-acid ethyl esters are an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia. More recent clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils, or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease. For all patients, it may be reasonable to recommend omega-3-acid ethyl esters for cardiovascular disease risk reduction.[1,18,20,24]

The American College of Cardiology/American Heart Association (ACC/AHA) released updated guidelines in 2013 which support initiating a statin in patients with established atherosclerotic cardiovascular disease (ASCVD). According to these recommendations, percent reduction in LDL-C is an indicator of response and adherence to therapy but treating to a targeted level is not a primary goal.[22] Combination therapy can be considered on an individual basis, but studies of combination therapy have generally not shown benefit beyond statin monotherapy. Additionally, if patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.[22] The 2018 ACC/AHA Guideline on the Management of Blood Cholesterol recommend using an LDL-C threshold of 70 mg/dL to consider the addition of non-statins to statin therapy in very high-risk ASCVD patients.[21] The ACC/AHA guidelines state that randomized controlled trial evidence show that use of therapy (e.g., niacin) to additionally lower non-HDL–C, once an LDL–C target was achieved, did not further reduce ASCVD outcomes. Of note, this guideline solely looks at the treatment of cholesterol for the primary and secondary prevention of ASCVD, and future updates are expected to provide guidance on the management of complex lipid disorders.[22]

Clinical trials have demonstrated that niacin positively impacts a variety of lipid/lipoprotein parameters.[49-66] Niacin has been shown to reduce the risk of recurrent nonfatal myocardial infarction in patients with hypercholesterolemia, as well as slow the progression or promote regression of atherosclerotic disease (in combination with bile acid sequestrants) in patients with a history of coronary artery disease and hypercholesterolemia.[86,87,98] The 3-year AIM-HIGH trial found no difference in the primary composite cardiovascular outcome end point between the niacin group (16.4%) and placebo group (16.2%).[91] There are limited head-to-head studies comparing the efficacy and safety of the different niacin formulations.[55-57] While flushing may be more common with the immediate-release formulation, it still occurs with the sustained-release and extended-release products. Cases of severe hepatic toxicity have occurred in patients who have substituted sustained-release niacin products for immediate-release niacin at equivalent doses.[2-4] Due to significant safety concerns, the American Heart Association stresses that dietary supplement niacin must not be used as a substitute for prescription niacin due to the potential for serious side effects.[16]

Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.[68-84] The GISSI-Prevenzione trial demonstrated the beneficial effects of omega-3 acid ethyl esters in patients who have experienced a recent myocardial infarction with omega-3 acid ethyl esters significantly reducing the risk of death, nonfatal myocardial infarction, and nonfatal stroke compared to vitamin E.[104] Icosapent ethyl is recommended in addition to a statin in patients with established ASCVD or diabetes and triglycerides from 135 to 499 ng/dL to prevent ASCVD events.[19] Two placebo-controlled icosapent ethyl trials (MARINE and ANCHOR) suggest that the drug significantly decreases triglyceride levels without increasing LDL-C levels.[37,38] The REDUCE-IT trial showed that use of icosapent ethyl 2 grams twice daily led to a greater reduction in triglycerides, cardiovascular events, and cardiovascular death compared to use of placebo among patients with

high triglycerides and either known cardiovascular disease or those at high risk for developing it, and who were already on statin therapy with relatively well-controlled LDL levels.[45] Studies of lomitapide in combination with other lipid-lowering therapies have shown a reduction in LDL-C from baseline of 35 to 50%.[45,46] Lomitapide carries a boxed warning regarding the risk of hepatotoxicity and is only available through a Risk Evaluation and Mitigation Strategy (REMS) program and should only be used as adjunctive therapy in patients with HoFH.[11]

Clinical trials have demonstrated that, when compared to placebo, bempedoic acid can effectively lower LDL-C and reduce other lipid/lipoprotein parameters in patients with HeFH. The CLEAR Wisdom trial demonstrated the efficacy of bempedoic acid in patients stable on maximally tolerated lipid-lowering therapy while the CLEAR Serenity trial demonstrated the efficacy of bempedoic acid in statin intolerant patients.[31,32] Studies of bempedoic acid in combination with ezetimibe have shown that bempedoic acid/ezetimibe can reduce LDL-C and other lipid/lipoprotein parameters in patients with HeFH when compared to placebo, bempedoic acid, or ezetimibe alone.[34,35] The ELIPSE HoFH trial demonstrated that evinacumab-dgnb, as adjunct therapy in patients with HoFH, can reduce LDL-C and improve lipid/lipoprotein parameters when compared to placebo.[36]

Leqvio® (inclisiran) is a first-in-class small interfering RNA directed to PCSK9 mRNA. It is FDA-approved for use as an adjunct to diet and statin therapy in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C. Leqvio® (inclisiran) is administered by a healthcare professional as a twice-yearly subcutaneous injection.[13] Studies of inclisiran have shown that it can reduce LDL-C by approximately 40 to 50%.[43-44] The American College of Cardiology: Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2022) list the newer agents (PCSK9 inhibitors, bempedoic acid, inclisiran, evinacumab, lomitapide) as potential considerations for adults with clinical ASCVD on statin therapy for secondary prevention and adults without clinical ASCVD and with baseline LDL-C ≥190 mg/dl not due to secondary causes, on statin therapy for primary prevention.[29]

Prescription niacin products offer significant clinical advantages in general use over the other brand, generic, and OTC niacin products in the same class (if applicable) but are comparable to each other. Extended-release niacin is available in a generic formulation. Due to their limited FDA-approved indications, prescription omega-3 acid ethyl esters and icosapent ethyl should be available through the medical justification portion of the prior authorization process for adults with severe hypertriglyceridemia (≥500 mg/dL). Omega-3 acid ethyl esters and icosapent ethyl are available in generic formulations. Due to the limited FDA-approved indications, lomitapide, evinacumab, and inclisiran should be available through the medical justification portion of the prior authorization process for use to diet and other lipid-lowering treatments in patients with HoFH.

XI. Recommendations

No brand miscellaneous antilipemic agent 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Nitrates and Nitrites
AHFS Class 241208
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I. Overview

Angina occurs when myocardial oxygen demand exceeds supply, which results in chest discomfort or pain. Common treatments for chronic angina include nitrates, β-blockers, and calcium channel blockers.[1] The nitrites and nitrates reduce oxygen demand by decreasing left ventricular pressure and systemic vascular resistance, as well as by dilating coronary arteries.[2-7] β-blockers reduce heart rate and contractility by competitively blocking the response to beta-adrenergic stimulation in the heart. Calcium channel blockers increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction, and reducing contractility. They also decrease oxygen demand by reducing systemic vascular resistance and arterial pressure.[8,9]

Tolerance develops after chronic exposure to nitrates, regardless of the route of administration or formulation used. This can be overcome by instituting short periods (10 to 12 hours) of withdrawal from nitrate therapy.[2-9] For example: administer the last dose of a short-acting product prior to 7:00 p.m., administer products twice daily instead of four times daily, or use sustained-release products once daily in the morning.[8,9]

The nitrates and nitrites 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 2022.

Table 1. Nitrates and Nitrites Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Isosorbide dinitrate	tablet	Isordil®*, Isordil Titradose®*	isosorbide dinitrate
Isosorbide mononitrate	extended-release tablet, tablet	N/A	isosorbide mononitrate
Nitroglycerin	injection, ointment, sublingual powder, sublingual tablet, transdermal patch, translingual spray	GoNitro®, Nitro-Bid®, Nitro-Dur®*, Nitrolingual®*, Nitrostat®*	Nitro-Bid®, Nitrostat®*, nitroglycerin

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the nitrates and nitrites are summarized in Table 2.

Table 2. Treatment Guidelines Using the Nitrates and Nitrites

Clinical Guideline	Recommendation(s)
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society	<u>Medical therapy to prevent MI and death in patients with stable IHD</u> • Aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications. • Treatment with clopidogrel is a reasonable option when aspirin in contraindicated. • Dipyridamole should not be used as antiplatelet therapy. • Beta-blocker therapy should be initiated and continued for three years in all patients with normal left ventricular (LV) function following MI or acute coronary syndromes.

Clinical Guideline	Recommendation(s)
of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)[10]**	• Metoprolol succinate, carvedilol, or bisoprolol should be used for all patients with systolic LV dysfunction (ejection fraction ≤40%) with heart failure or prior MI, unless contraindicated. • ACE inhibitors should be prescribed in all patients with stable IHD who also have hypertension, diabetes, LV systolic dysfunction (ejection fraction ≤40%), and/or chronic kidney disease, unless contraindicated. • Angiotensin-receptor blockers (ARBs) are recommended for patients with stable IHD who have hypertension, diabetes, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. • Patients should receive an annual influenza vaccine. <u>Medical therapy for relief of symptoms in patients with stable IHD</u> • Beta-blockers are recommended as initial therapy for relief of symptoms. • Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects. • Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful. • Nitroglycerin or nitroglycerin spray should be used for immediate relief of angina. • Ranolazine is a fourth-line agent reserved for patients who have contraindications to, do not respond to, or cannot tolerate β-blockers, calcium-channel blockers, or long-acting nitrates.

European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with Persistent ST-segment Elevation (2017)[11]**	<u>Periprocedural pharmacotherapy</u>
	• Platelet inhibition
	  ○ Patients undergoing primary percutaneous coronary intervention (PCI) should receive dual antiplatelet therapy (DAPT), a combination of aspirin and a $P2Y_{12}$ inhibitor, and a parenteral anticoagulant.
	  ○ A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.
	  ○ Aspirin (oral of intravenous if unable to swallow) is recommended as soon as possible for all patients without contraindications.
	  ○ GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.
	  ○ Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.
	• Anticoagulant therapy
	  ○ Anticoagulant options for primary PCI include unfractionated heparin (UFH), enoxaparin, and bivalirudin.
	  ○ Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.
	  ○ Routine use of UFH is recommended.
	  ○ In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.
	  ○ Routine use of enoxaparin intravenous should be considered.
	  ○ Routine use of bivalirudin should be considered.
	  ○ Fondaparinux is not recommended for primary PCI.
	
	<u>Maintenance antithrombotic strategy after ST-elevation myocardial infarction</u>
	• Antiplatelet therapy with low-dose aspirin (75 to 100 mg) is indicated.
	• DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended

Clinical Guideline	Recommendation(s)
	for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy should be considered for one to six months (according to a balance between the estimated risk of recurrent coronary events and bleeding). • DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding. • In patients with left ventricular (LV) thrombus, anticoagulation should be administered for up to six months guided by repeated imaging. • In high ischemic-risk patients who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice daily on top of aspirin for longer than 12 months may be considered for up to three years. • In low bleeding risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. <u>Routine therapies in the acute, subacute, and long-term phases</u> • Beta-blockers o Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF ≤40% unless contraindicated. o Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with no signs of acute heart failure, and with an SBP >120 mmHg. o Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindication. o Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia. • Lipid-lowering therapies o It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term. o An LDL-C goal of <70 mg/dL or a reduction of at least 50% if the baseline LDL-C is between 70 to 135 mg/dL is recommended. o It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation. o In patients with LDL-C ≥70 mg/dL despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. • ACE inhibitors/ARBs o ACE inhibitors are recommended, starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct. o An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors.

Clinical Guideline	Recommendation(s)
	○ ACE inhibitors should be considered in all patients in the absence of contraindications. • Mineralocorticoid receptor antagonists ○ Mineralocorticoid receptor antagonists are recommended in patients with an LVEF ≤40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalemia.
American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[12]**	<u>Early hospital care- standard medical therapies</u> • Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. • Anti-ischemic and analgesic medications ○ Nitrates ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. ○ Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use ○ Beta-adrenergic blockers ▪ Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue beta-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to beta-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. ○ Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of beta-clockers and nitrates.

Clinical Guideline	Recommendation(s)
	▪ CCBs are recommended for ischemic symptoms when beta-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg

Clinical Guideline	Recommendation(s)
	non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed

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	about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2020)[13]**	<u>Pharmacological treatment of ischemia</u> • Sublingual or intravenous nitrates and early initiation of beta-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • Continuation of chronic beta-blocker therapy is recommended unless the patient is in overt heart failure • Sublingual or intravenous nitrates are recommended to relieve angina; intravenous treatment is recommended in patients with recurrent angina, uncontrolled hypertension, or signs of heart failure. • In patients with suspected/confirmed vasospastic angina, calcium channel blockers, and nitrates should be considered and beta-blockers avoided. <u>Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes</u> • Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150 to 300 mg (in aspirin-naïve patients) and a maintenance dose of 75 to 100 mg/day long-term regardless of treatment strategy. • A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risks of bleeds. o Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindication, for all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which

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	should be discontinued when ticagrelor is started). ○ Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. Prasugrel should be considered in preference to ticagrelor in NSTE-ACS patients who proceed to PCI. ○ Clopidogrel (300 to 600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation. • $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after DES implantation may be considered in patients deemed at high bleeding risk. • Pre-treatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy. • It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known. • It is not recommended to administer prasugrel in patients whom coronary anatomy is not known. • GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications. • Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI. • It is not recommended to administer GPIIb/IIIa inhibitors in patients whom coronary anatomy is not known. • $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of the ischemic and bleeding risks of the patient. <u>Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes</u> • Parenteral anticoagulation is recommended at the time of diagnosis according to both ischemic and bleeding risks. • Fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy. • Bivalirudin is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI. • UFH is recommended in patients undergoing PCI who did not receive any anticoagulant. • In patients on fondaparinux undergoing PCI, a single intravenous bolus of UFH is recommended during the procedure. • Enoxaparin or UFH are recommended when fondaparinux is not available. • Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated for PCI with subcutaneous enoxaparin. • Additional activated clotting time-guided intravenous boluses of UFH during PCI may be considered following initial UFH treatment. • Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated. • Crossover between UFH and LMWH is not recommended. • In NSTEMI patients with no prior stroke/TIA and at high ischemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation. <u>Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation</u> • In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a $CHADS_2$-VASc score ≥ 2, recent VTE, mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. • An early invasive coronary angiography (within 24 hours) should be considered

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	in moderate- to high-risk patients, irrespective of oral anticoagulant exposure, to expedite treatment allocation (medical vs PCI vs CABG) and to determine optimal antithrombotic regimen. • Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to oral anticoagulation before coronary angiography is not recommended. • During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all non-vitamin K antagonist oral anticoagulants (NOACs) and if INR is <2.5 in VKA-treated patients. • Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. • Periprocedural DAPT administration consisting of aspirin and clopidogrel up to one week is recommended • Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months • Following coronary stenting, dual (oral) antiplatelet therapy (DAPT) including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with non-ST-elevation acute coronary syndromes and atrial fibrillation with a $CHADS_2$-VASc score of 1 (in males) or 2 (in females). • If at low bleeding risk (HAS-BLED ≤2), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for six months, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months. • If at high bleeding risk (HAS-BLED ≥3), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for one month, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months irrespective of the stent type. • Dual therapy with oral anticoagulant and clopidogrel may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis). • The use of ticagrelor or prasugrel as part of triple therapy is not recommended. • In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year. <u>Recommendations for post-interventional and maintenance treatment</u> • In patients with NSTE-ACS with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding. • Adding a second anti-thrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a moderate to high risk of ischemic events and without increased risk of major bleeding. • After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after three months should be considered • After stent implantation in patients undergoing DAPT, stopping aspirin after three to six months should be considered, depending on balance between ischemic and bleeding risk. • De-escalation of $P2Y_{12}$ inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.
American College of Cardiology Foundation/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction**	<u>Antiplatelet therapy to support primary PCI for STEMI</u> • Aspirin 162 to 325 mg should be given before primary PCI. • After PCI, aspirin should be continued indefinitely. • A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg. • $P2Y_{12}$ inhibitor therapy should be given for one year to patients with STEMI who receive a stent (bare-metal or drug-eluting) during primary PCI using

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(2013)[14]	clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily. • It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI. • It is reasonable to start treatment with an IV GP IIb/IIIa receptor antagonist such as abciximab, high bolus-dose tirofiban or double-bolus eptifibatide at the time of primary PCI (with or without stenting or clopidogrel pre-treatment) in selected patients with STEMI who are receiving UFH. • It may be reasonable to administer IV GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended. • It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI. • Continuation of a $P2Y_{12}$ inhibitor beyond one year may be considered in patients undergoing drug-eluting stent placement. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. <u>Anticoagulant therapy to support primary PCI</u> • For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended: UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered or bivalirudin with or without prior treatment with UFH. • In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist. • Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis. <u>Adjunctive antiplatelet therapy with fibrinolysis</u> • Aspirin (162- to 325-mg loading dose) and clopidogrel (300 mg loading dose for ≤75 year of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy. • Aspirin should be continued indefinitely and clopidogrel (75 mg daily) should be continued for at least 14 days and up to one year in patients with STEMI who receive fibrinolytic therapy. • It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses after fibrinolytic therapy. <u>Adjunctive anticoagulant therapy with fibrinolysis</u> • Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the hospitalization, up to eight days or until revascularization if performed. • Recommended regimens include UFH administered as a weight-adjusted IV bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularization; enoxaparin administered according to age, weight, and creatinine clearance, given as an IV bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to eight days or until revascularization; or fondaparinux administered with initial IV dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 mL/min, for the duration of the index hospitalization, up to eight days or until revascularization. <u>Antiplatelet therapy to support PCI after fibrinolytic therapy</u>

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	• After PCI, aspirin should be continued indefinitely. • Clopidogrel should be provided as a 300 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy; a 600 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy; and a dose of 75 mg daily should be given after PCI. • After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses. • Prasugrel, in a 60 mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent. • Prasugrel, in a 10 mg daily maintenance dose, is reasonable after PCI. • Prasugrel should not be administered to patients with a history of prior stroke or TIA. Anticoagulant therapy to support PCI after fibrinolytic therapy • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with IV UFH, additional boluses of IV UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered. • For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior eight hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between eight and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given.
American College of Cardiology Foundation/ American Heart Association: **AHA/ACC/HFSA Guideline for the Management of Heart Failure (2022)**[15]	ACCF/AHA Stages of Heart Failure (HF) • Stage A: At high risk for HF but without symptoms, structural heart disease or cardiac biomarkers of stretch or injury. • Stage B: Structural heart disease, evidence for increased filling pressures or patients with risk factors, but without signs or symptoms of HF. • Stage C: Structural heart disease with prior or current symptoms of HF. • Stage D: Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize guideline directed medical therapy. Recommendations for Patients at Risk for HF (Stage A: Primary Prevention) • In patients with hypertension, blood pressure should be controlled in accordance with GDMT for hypertension to prevent symptomatic HF. • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT2i should be used to prevent hospitalizations for HF. • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. • For patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing guideline directed medical therapy, can be useful to prevent the development of LV dysfunction or new onset HF. • In the general population, validated multivariable risk scores can be useful to estimate subsequent risk of incident HF. Recommendations for Management of Stage B: Preventing the Syndrome of Clinical HF in Patients With Pre-HF

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	• In patients with LVEF ≤40%, ACE inhibitor should be used to prevent symptomatic HF and reduce mortality. • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. • In patients with a recent MI and LVEF ≤40% who are intolerant to ACE inhibitor, ARB should be used to prevent symptomatic HF and reduce mortality. • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline directed medical therapy and have reasonable expectation of meaningful survival for >1 year, an ICD is recommended for primary prevention of sudden cardiac death to reduce total mortality. • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. • In patients with LVEF <50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. • In patients with LVEF <50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. <u>Recommendations for Management of Stage C HF</u> • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms and prevent worsening HF. • For patients with HF and congestive symptoms, addition of a thiazide to treatment with a loop diuretic should be reserved for patients who do not respond to moderate- or high-dose loop diuretics to minimize electrolyte abnormalities. • In patients with HFrEF and NYHA class II to III symptoms, the use of ARN inhibitor is recommended to reduce morbidity and mortality. • In patients with previous or current symptoms of chronic HFrEF, the use of ACE inhibitor is beneficial to reduce morbidity and mortality when the use of ARN inhibitor is not feasible. • In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACE inhibitor because of cough or angioedema and when the use of ARN inhibitor is not feasible, the use of ARB is recommended to reduce morbidity and mortality. • In patients with previous or current symptoms of chronic HFrEF, in whom ARN inhibitor is not feasible, treatment with an ACE inhibitor or ARB provides high economic value. • In patients with chronic symptomatic HFrEF NHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARN inhibitor is recommended to further reduce morbidity and mortality. • In patients with chronic symptomatic HFrEF, treatment with an ARN inhibitor instead of an ACE inhibitor provides high economic value. • ARN inhibitor should not be administered concomitantly with ACE inhibitor or within 36 hours of the last dose of an ACE inhibitor. • ARN inhibitor should not be administered to patients with any history of angioedema. • ACE inhibitor should not be administered to patients with any history of angioedema. • In patients with HFrEF, with current or previous symptoms, use of one of the three beta blockers proven to reduce mortality (bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. • In patients with HFrEF, with current or previous symptoms beta-blocker therapy provides high economic value. • In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and

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	mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. • In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value. • In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia. • In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. • In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value. • For patients self-identified as African American with NYHA class III to IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptom and reduce morbidity and mortality. • For patients self-identified as African American with NYHA class III to IV HFrEF who are receiving optimal medical therapy with ACE inhibitor or ARB, beta blockers and MRA, the combination of hydralazine and isosorbide dinitrate provides high economic value. • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARN inhibitor, ACE inhibitor or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. • In patients with HF who experience hyperkalemia while taking a renin-angiotensin-aldosterone system inhibitor (RAASi), the effectiveness of potassium binders to improve outcomes by facilitating continuation of RAASi therapy is uncertain. • In patients with chronic HFrEF without a specific indication, anticoagulation is not recommended. • For patients with symptomatic stable chronic HFrEF who are receiving guideline directed medical therapy, including beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 bpm at rest, ivabradine can be beneficial to reduce HF hospitalization and cardiovascular death. • In patients with symptomatic HFrEF despite guideline directed medical therapy, digoxin might be considered to decrease hospitalization for HF. • In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. • In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. • Among patients with current or previous symptomatic HFmrEF, use of evidence-based beta blockers for HFrEF, ARN inhibitor, ACE inhibitor or ARB ad MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. • In patients with HF with improved EF after treatment, guideline directed medical therapy should be continued to prevent relapse of heart failure and LV dysfunction, even in patients who may become asymptomatic. • Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. • In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.

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	• In patients with HFpEF, management of AF can be useful to improve symptoms. • In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. • In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. • In selected patients with HFpEF, ARN inhibitor may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. • In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective. • In select patients with wild-type or variant trans-thyretin cardiac amyloidosis and NYHA class I to III HF symptoms, transthyretin tetramer stabilizer therapy (tafamidis) is indicated to reduce cardiovascular morbidity and mortality. • At 2020 list prices, tafamidis provides low economic value in patients with HF with wild-type or variant transthyretin cardiac amyloidosis. • In patients with cardiac amyloidosis and AF, anticoagulation is reasonable to reduce the risk of stroke regardless of the congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category score. <u>Recommendations for Management of Stage D HF</u> • In patients with advanced HF refractory to guideline directed medical therapy and device therapy who are eligible and awaiting MCS or cardiac transplantation, continuous intravenous inotropic support is reasonable as bridge therapy. • In select patients with stage D HF, despite optimal guideline directed medical therapy and device therapy who are ineligible for either MCS or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. • In patients with HF, long-term use of either continuous or intermittent intravenous inotropic agents, for reasons other than palliative care or as bridge to advanced therapies, is potentially harmful.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[16]	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or

Clinical Guideline	Recommendation(s)
	ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a beta-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a beta-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u>

Clinical Guideline	Recommendation(s)
	• Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk • of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.

National Institute for Health and Clinical Excellence: **Chronic heart failure in adults: management (2018)**[17]	<u>Treating heart failure with reduced ejection fraction</u>
	• First-line treatment
	  ○ Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have heart failure with reduced ejection fraction.
	• ACE inhibitors
	  ○ Do not offer ACE inhibitor therapy if there is a clinical suspicion of hemodynamically significant valve disease until the valve disease has been assessed by a specialist.
	  ○ Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every two weeks) until the target or maximum tolerated dose is reached.
	  ○ Measure serum sodium and potassium, and assess renal function, before and one to two weeks after starting an ACE inhibitor, and after each dose increment.
	  ○ Measure blood pressure before and after each dose increment of an ACE inhibitor.
	  ○ Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell.
	• Alternative treatments if ACE inhibitors are not tolerated

Clinical Guideline	Recommendation(s)
	○ Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side effects with ACE inhibitors. ○ Measure serum sodium and potassium, and assess renal function, before and after starting an ARB and after each dose increment. ○ Measure blood pressure after each dose increment of an ARB. ○ Once the target or maximum tolerated dose of an ARB is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell. ○ If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have heart failure with reduced ejection fraction. • Beta-blockers ○ Do not withhold treatment with a beta-blocker solely because of age or the presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. ○ Introduce beta-blockers in a 'start low, go slow' manner. Assess heart rate and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. ○ Switch people whose condition is stable and who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. • Mineralocorticoid receptor antagonists (MRAs) ○ Offer an MRA, in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. ○ Measure serum sodium and potassium, and assess renal function, before and after starting an MRA and after each dose increment. ○ Measure blood pressure before and after each dose increment of an MRA. ○ Once the target, or maximum tolerated, dose of an MRA is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell. • Specialist treatment ○ Ivabradine is recommended as an option for treating chronic heart failure for people: ▪ with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and ▪ who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and ▪ who are given ivabradine in combination with standard therapy including beta-blocker therapy, ACE inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and ▪ with a left ventricular ejection fraction of 35% or less. ○ Ivabradine should only be initiated after a stabilization period of four weeks on optimized standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. ○ Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. ○ Sacubitril-valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: ▪ with New York Heart Association (NYHA) class II to IV symptoms and

Clinical Guideline	Recommendation(s)
	▪ with a left ventricular ejection fraction of 35% or less and ▪ who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or ARBs. o Treatment with sacubitril-valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. o Hydralazine in combination with nitrate ▪ Seek specialist advice and consider offering hydralazine in combination with nitrate (especially if the person is of African or Caribbean family origin and has moderate to severe heart failure [NYHA class III/IV] with reduced ejection fraction). o Digoxin ▪ Digoxin is recommended for worsening or severe heart failure with reduced ejection fraction despite first-line treatment for heart failure. Seek specialist advice before initiating. ▪ Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within eight to 12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence. ▪ The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. <u>Treating heart failure with reduced ejection fraction in people with chronic kidney disease</u> • For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR of 30 ml/min/1.73 m^2 or above: o offer the treatment outlined above and o if the person's eGFR is 45 ml/min/1.73 m^2 or below, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, MRAs and digoxin. • For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR below 30 ml/min/1.73 m^2, the specialist heart failure multidisciplinary team should consider liaising with a renal physician. • Monitor the response to titration of medicines closely in people who have heart failure with reduced ejection fraction and chronic kidney disease, taking into account the increased risk of hyperkalemia. <u>Managing all types of heart failure: Pharmacological treatment</u> • Diuretics o Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. o People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice. • Calcium-channel blockers o Avoid verapamil, diltiazem and short-acting dihydropyridine agents in people who have heart failure with reduced ejection fraction. • Amiodarone o Make the decision to prescribe amiodarone in consultation with a specialist. o Review the need to continue the amiodarone prescription at the six-monthly clinical review. o Offer people taking amiodarone liver and thyroid function tests, and a review of side effects, as part of their routine 6-monthly clinical review.

Clinical Guideline	Recommendation(s)

	• Anticoagulants
	  ○ For people who have heart failure and atrial fibrillation, follow the recommendations on anticoagulation in the NICE guideline on atrial fibrillation. Be aware of the effects of impaired renal and liver function on anticoagulant therapies.
	  ○ In people with heart failure in sinus rhythm, anticoagulation should be considered for those with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus.
	• Vaccinations
	  ○ Offer people with heart failure an annual vaccination against influenza.
	  ○ Offer people with heart failure vaccination against pneumococcal disease (only required once).
	• Contraception and pregnancy
	  ○ In women of childbearing potential who have heart failure, contraception and pregnancy should be discussed. If pregnancy is being considered or occurs, specialist advice should be sought. Subsequently, specialist care should be shared between the cardiologist and obstetrician.

European Society of Cardiology: **Guidelines on Cardiovascular Assessment and Management of Patients Undergoing Non-Cardiac Surgery (2022)**[18]	• For patients with hypertensive emergencies, the 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend labetalol, nitroglycerin, nitroprusside, etc., according to the affected organ.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the nitrates and nitrites 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 Nitrates and Nitrites[2-9]

Indication	Isosorbide Dinitrate*	Isosorbide Mononitrate*	Nitroglycerin		
			Lingual spray/ Sublingual tablet/ Sublingual powder	Injection	Topical/ Transdermal*
Angina Pectoris					
Acute relief of an attack of angina pectoris			✔		
Prevention of angina pectoris due to coronary artery disease	✔	✔	✔		✔
Treatment of angina pectoris due to coronary artery disease	✔ (sublingual tablet)	✔ (tablet)		✔ †	
Cardiovascular Uses					
Control of congestive heart failure in the setting of acute myocardial infarction				✔	
Induction of intraoperative hypotension				✔	
Treatment of perioperative hypertension				✔	

*The onset of action of this product is not sufficiently rapid for it to be useful in aborting an acute attack.
†In patients who have not responded to sublingual nitroglycerin and beta-blockers.

IV. Pharmacokinetics

The pharmacokinetic parameters of the nitrates and nitrites are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Nitrates and Nitrites[9]

Generic Name(s)	Bioavailability (%)	Onset (minutes)	Duration	Excretion (%)	Half-Life
Isosorbide dinitrate	ER: 22 IR: 10 to 90 SL: 19 to 93	SL: 2 to 10	IR: 8 hours SL: 1 to 2 hours	Renal (80 to 90) Feces (limited; % not reported)	ER: 4 hours IR: 4 hours SL: 1 hour
Isosorbide mononitrate	ER: 80 to 100 IR: 93 to 100	ER: 45 to 60 IR: 45 to 60	ER: 6 hours IR: 6 hours	Renal (78) Feces (1)	ER: 6 hours IR: 6 hours
Nitroglycerin	Patch: 75* SL: 38.5	Oint: 30 to 60 SL: 1 to 3	Oint: 7 hours Patch: 8 to 10 hours SL: up to 60 minutes	Renal (22)	1.5 to 7.5 minutes

*Compared to intravenous dosing.
ER=extended-release, IR=immediate-release, Oint=ointment, SL=sublingual

V. Drug Interactions

Major drug interactions with the nitrates and nitrites are listed in Table 5.

Table 5. Major Drug Interactions with the Nitrates and Nitrites[9]

Generic Name(s)	Interaction	Mechanism
Isosorbide dinitrate, Isosorbide mononitrate, Nitroglycerin	Avanafil	Avanafil potentiates the hypotensive effects of nitrates, resulting in severe hypotension.
Isosorbide dinitrate, Isosorbide mononitrate, Nitroglycerin	Sildenafil, tadalafil, vardenafil	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.
Isosorbide dinitrate, Isosorbide mononitrate, Nitroglycerin	Riociguat	Riociguat potentiates the hypotensive effects of nitrates, resulting in severe hypotension.
Nitroglycerin	Alteplase	Concentrations of tissue-type plasminogen activator (tPA) are decreased, indicating impairment of the thrombolytic effect of alteplase. The enhanced hepatic blood flow as a result of the nitroglycerin facilitates the hepatic metabolism of tPA.
Nitroglycerin	Heparin	Concurrent use of heparin and nitroglycerin may result in a decrease in partial thromboplastin time.

VI. Adverse Drug Events

The most common adverse drug events reported with the nitrates and nitrites are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Nitrates and Nitrites[2-9]

Adverse Events	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Cardiovascular				
Abnormal heart sound	-	≤5	-	-
Aggravated angina pectoris	-	≤5	-	-
Angina pectoris	-	-	≥1	-
Arrhythmia	-	≤5	<1	-
Atrial fibrillation	-	≤5	<1	-
Bradycardia	-	≤5	-	-

Adverse Events	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Bundle branch block	-	≤5	-	-
Cardiac failure	-	≤5	-	-
Crescendo angina	✔	-	-	✔
Extrasystole	-	≤5	-	-
Flushing	-	≤5	-	✔
Heart murmur	-	≤5	-	-
Hypertension	-	≤5	-	-
Hypotension	✔	≤5	<1	4
Migraine	-	≤5	-	-
Myocardial infarction	-	≤5	✔	-
Palpitation	-	≤5	<1	✔
Postural hypotension	✔	-	<1	✔
Premature ventricular contraction	-	-	<1	-
Q wave abnormality	-	≤5	-	-
Rebound hypertension	✔	-	-	✔
Supraventricular tachycardia	-	-	<1	-
Syncope	✔	✔	<1	✔
Tachyarrhythmia	-	-	-	-
Tachycardia	-	≤5	-	-
Ventricular tachycardia	-	≤5	-	-
Central Nervous System				
Anxiety	-	≤5	<1	-
Confusion	-	≤5	<1	-
Decreased libido	-	≤5	-	-
Depression	-	≤5	-	-
Dizziness	✔	8 to 11	3 to 5	≥2
Headache	✔	≥5	19 to 38	50 to 63
Impotence	-	≤5	<1	-
Insomnia	-	≤5	<1	-
Lightheadedness	✔	-	-	6
Nervousness	-	≤5	<1	-
Neuritis	-	≤5	-	-
Paresis	-	≤5	-	-
Paresthesia	-	≤5	-	≥2
Purpura	-	≤5	-	-
Somnolence	-	≤5	-	-
Vertigo	-	≤5	-	✔
Dermatological				
Acne	-	≤5	-	-
Anaphylactoid reactions	-	-	-	✔
Contact dermatitis	-	-	-	✔ *
Exfoliative dermatitis	-	-	-	✔
Photophobia	-	≤5	-	-
Pruritus	-	≤5	<1	-
Rash	-	≤5	<1	✔
Skin nodule	-	≤5	-	-
Gastrointestinal				
Abdominal pain	-	≤5	<1	≤2
Constipation	-	≤5	-	-
Diarrhea	-	≤5	<1	-
Dyspepsia	-	≤5	<1	-
Flatulence	-	≤5	-	-
Gastric ulcer	-	≤5	-	-

Adverse Events	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Gastritis	-	≤5	-	-
Hemorrhagic gastric ulcer	-	≤5	-	-
Loose stools	-	≤5	-	-
Nausea	-	≤5	2 to 4	✔
Vomiting	-	≤5	2 to 4	✔
Genitourinary				
Dysuria	-	-	<1	-
Polyuria	-	≤5	-	-
Renal calculus	-	≤5	-	-
Urinary tract infection	-	≤5	-	-
Hematologic				
Hemolytic anemia	-	-	-	-
Hypochromic anemia	-	≤5	-	-
Methemoglobinemia	✔	✔	✔	✔
Thrombocytopenia	-	≤5	-	-
Laboratory Test Abnormalities				
Elevated SGOT	-	≤5	-	-
Elevated SGPT	-	≤5	-	-
Musculoskeletal				
Arthralgia	-	≤5	<1	-
Asthenia	-	≤5	<1	-
Muscle weakness	-	≤5	-	-
Musculoskeletal pain	-	≤5	-	-
Myalgia	-	≤5	-	-
Respiratory				
Bronchitis	-	≤5	<1	-
Bronchospasm	-	≤5	-	-
Coughing	-	≤5	-	-
Dyspnea	-	≤5	-	≤2
Increased sputum	-	≤5	-	-
Nasal congestion	-	≤5	-	-
Pharyngitis	-	≤5	-	-
Pneumonia	-	≤5	<1	-
Pulmonary infiltration	-	≤5	-	-
Rales	-	≤5	-	-
Rhinitis	-	≤5	-	-
Sinusitis	-	≤5	-	-
Upper respiratory tract infection	-	-	<1	-
Other				
Abnormal hair texture	-	≤5	-	-
Abnormal vision	-	≤5	-	-
Agitation	-	-	<1	-
Atrophic vaginitis	-	≤5	-	-
Back pain	-	≤5	-	-
Bacterial infection	-	≤5	-	-
Blurred vision	✔	-	<1	-
Breast pain	-	≤5	-	-
Chest pain	-	≤5	-	-
Cold sweat	-	-	<1	-
Collapse	-	-	-	✔
Conjunctivitis	-	≤5	-	-
Diplopia	-	-	<1	-
Dry mouth	-	≤5	-	-

Adverse Events	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Discoordination	-	-	<1	-
Earache	-	≤5	-	-
Edema	-	≤5	<1	-
Fatigue	-	≤5	-	-
Fever	-	≤5	-	-
Flu-like symptoms	-	≤5	-	-
Frozen shoulder	-	≤5	-	-
Glossitis	-	≤5	-	-
Hemorrhoids	-	≤5	-	-
Hot flashes	-	≤5	-	-
Hyperuricemia	-	≤5	-	-
Hypoesthesia	-	≤5	<1	-
Hypokalemia	-	≤5	-	-
Hypokinesia	-	-	<1	-
Impaired concentration	-	≤5	-	-
Increased appetite	-	-	<1	-
Increased sweating	-	≤5	-	-
Intermittent claudication	-	≤5	-	-
Leg ulcer	-	≤5	-	-
Malaise	-	≤5	<1	-
Melena	-	≤5	-	-
Moniliasis	-	≤5	-	-
Myositis	-	≤5	-	-
Nightmares	-	-	<1	-
Pallor	-	-	-	✔
Paroniria	-	≤5	-	-
Ptosis	-	≤5	-	-
Restlessness	-	-	-	✔
Rigors	-	≤5	<1	-
Tendon disorder	-	≤5	-	-
Tenesmus	-	-	<1	-
Tinnitus	-	≤5	-	-
Tooth disorder	-	-	<1	-
Tremor	-	≤5	-	-
Tympanic membrane perforation	-	≤5	-	-
Varicose veins	-	≤5	-	-
Viral infection	-	≤5	-	-
Weakness	-	-	-	✔

IR=immediate-release, SR=sustained-release
*Topical formulation only.
✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the nitrates and nitrites are listed in Table 7.

Table 7. Usual Dosing Regimens for the Nitrates and Nitrites[2-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Isosorbide dinitrate	Angina pectoris: Extended-release capsule, extended-release tablet: initial, 40 mg/day; maintenance, 40 to 80 mg every 8 to	Safety and efficacy in children have not been established.	Tablet: 5 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	12 hours; maximum, 160 mg/day Sublingual tablet (treatment): initial, 2.5 to 5 mg; maintenance, titrate upward until angina is relieved or side effects limit the dose Sublingual tablet (prophylaxis): 2.5 to 5 mg approximately 15 minutes before the anticipated activity likely to cause angina is expected to begin* Tablet: initial, 5 to 20 mg two or three times daily; maintenance, 10 to 40 mg two or three times daily		
Isosorbide mononitrate	Angina pectoris: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, dosage may be increased to 120 mg once daily, 240 mg/day may be required Tablet: initial, 5 to 10 mg/day; maintenance, 20 mg twice daily, with the two doses administered seven hours apart	Safety and efficacy in children have not been established.	Extended-release tablet: 30 mg 60 mg 120 mg Tablet: 10 mg 20 mg
Nitroglycerin	Angina pectoris: Injection, ointment, sublingual tablet, transdermal patch, translingual spray: there is no fixed optimum dose Injection: 5 µg/min; increase 5 µg/min every 3 to 5 minutes until some response is noted; if no response at 20 µg/min, increase by 10 µg/min every 3 to 5 minutes, up to 200 µg/min; maximum, 400 µg/mL Ointment: ½ inch (1.3 cm, 7.5 mg) to 2 inches (5.1 cm, 30 mg) typically applied to 36 square inches of truncal skin Powder packet: one or two packets at the onset of an attack under the tongue, one additional packet may be administered every five minutes as needed, maximum of three packets are recommended within a 15-minute period Sublingual tablet: 1 tablet dissolved under the tongue or in the buccal pouch at the first sing of an acute attack; maintenance, the dose may be repeated approximately every 5	Safety and efficacy in children have not been established.	Injection: 0.1 mg/mL 0.2 mg/mL 0.4 mg/mL 5 mg/mL Ointment: 2% Powder packet: 0.4 mg Sublingual tablet: 0.3 mg 0.4 mg 0.6 mg Transdermal patch: 0.1 mg/hr 0.2 mg/hr 0.3 mg/hr 0.4 mg/hr 0.6 mg/hr 0.8 mg/hr Translingual spray: 0.4 mg/dose

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	minutes until relief is obtained; maximum, 3 tablets within a 15 minute period Transdermal patch: initial, 0.2 and 0.4 mg/hr; maintenance, 0.4 and 0.8 mg/hr; the appropriate dosing schedule would include a daily patch-on period of 12 to 14 hours and a daily patch-off period of 10 to 12 hours Translingual spray: 1 or 2 metered sprays administered onto or under the tongue at the onset of an attack; maximum, no more than 2 sprays are recommended within a 15 minute period <u>Congestive heart failure:</u> Injection: 5 µg/min; increase 5 µg/min every 3 to 5 minutes until some response is noted; if no response at 20 µg/min, increase by 10 µg/min every 3 to 5 minutes, up to 200 µg/min; maximum, 400 µg/mL <u>Intraoperative hypotension and perioperative hypertension:</u> Injection: 5 µg/min; increase 5 µg/min every 3 to 5 minutes until some response is noted; if no response at 20 µg/min, increase by 10 µg/min every 3 to 5 minutes, up to 200 µg/min; maximum, 400 µg/mL		

*Isosorbide dinitrate sublingual tablet may be used to abort an acute anginal episode, but its use is recommended only in patients who fail to respond to sublingual nitroglycerin.

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with the Nitrates and Nitrites

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chronic Stable Angina				
Parker et al.[19] (1993) ISMN 5 mg BID vs ISMN 10 mg BID vs ISMN 20 mg BID vs placebo	DB, PC, PG Patients with stable angina underwent testing prior to exercise as well as 2 and 7 hours after each dose on days 1 and 14. Additionally, on days 7 and 21, testing was performed 2 hours after the first dose.	N=214 3 weeks	Primary: Total exercise duration and time to moderate angina Secondary: Not reported	Primary: ISMN, at all doses, showed improvement over placebo at two and seven hours after the morning dose and two hours after the second dose on day one. Active treatment prolonged exercise duration over placebo at two hours postdose for each of the two daily doses. ISMN 20 mg was the only strength which demonstrated increased exercise duration seven hours after administration, which occurred on day 14. Overall, there were fewer episodes of angina noted in the ISMN 20 mg group. Secondary: Not reported
Thadani et al.[20] (1994) ISMN 20 mg BID vs placebo Patients were allowed to continue β-blocker therapy.	DB, MC, PC, PG, RCT Patients with stable exertional angina who stopped treadmill exercise secondary to angina pectoris	N=116 2 weeks	Primary: Total exercise duration (time to moderately severe angina) Secondary: ST-segment depression, heart rate, DBP and SBP, number of anginal attacks, number of nitroglycerin doses	Primary: A statistically significant improvement in total exercise duration was observed at both the morning and afternoon dose compared to placebo ($P<0.01$). Secondary: The magnitude of ST-segment depression was comparable in both the isosorbide-5-mononitrate and placebo groups (1.2±0.1 vs 1.2±0.2 mm; $P>0.2$). Heart rate and SBP, during the period of exercise, was determined to be similar among the groups. Additionally, the number of anginal attacks and doses of nitroglycerin were no different per group.
Chrysant et al.[21]	DB, RCT	N=313	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1993) ISMN ER 30 mg in the morning vs ISMN ER 60 mg in the morning vs ISMN ER 120 mg in the morning vs ISMN ER 240 mg in the morning vs placebo	Patients with stable effort-induced angina	6 weeks	Mean change from baseline in total exercise time (serial exercise testing immediately prior to and four and two hours after administration, on days one, seven, 14, 28 and 42) Secondary: Adverse effect	A significant improvement in mean total exercise time of 30 to 50 seconds was shown in all active-treatment groups compared to placebo at four and 12 hours postdose (P<0.01). The mean changes from baseline in total exercise time in patients on ISMN ER 120 mg or 240 mg surpassed placebo by about 50 to 60 seconds at 4 hours postdose (P<0.01), and by 30 to 35 seconds 12 hours after dosing (P≤0.05). There was no meaningful difference in response found between active treatment and placebo at 24 hours after administration, thus no indication that ISMN ER induced rebound angina. Secondary: The most common adverse effect among active treatment groups was transient headache.
Bray et al.[22] (1991) NTG administered buccally vs NTG administered sublingually	DB, MC Patients with proven chronic stable exercise-induced angina	N=Not reported Duration not reported	Primary: Efficacy Secondary: Not reported	Primary: The two formulations had comparable effects on acute attacks of angina pectoris. Secondary: Not reported
Ryden et al.[23] (1987) NTG administered	MC, XO Patients with stable angina pectoris	N=126 2 weeks	Primary: Efficacy Secondary:	Primary: Buccal NTG resulted in 31% less acute anginal attacks compared to the sublingual formulation (P<0.001). Prophylaxis was effective in 74% of patients taking buccal NTG compared to 66% of sublingual-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
buccally vs NTG administered sublingually			Ease of use, patient preference	patients (P<0.05). Secondary: There was no difference in ease of use reported in 67% of patients, whereas 19% indicated that sublingual NTG was easier and 14% buccal NTG. Overall, 65% of patients preferred buccal NTG and 19% preferred sublingual NTG (P<0.05). As far as prophylactic use, buccal administration was again preferred by more patients (81%) than sublingual use (4%; P<0.05).
Demots et al.[24] (1989) NTG 0.2 mg/hour or 0.4 mg/hour transdermal patch for 12 hours (Group A) vs NTG 0.6 mg/hour or 0.8mg/hour transdermal patch for 12 hours (Group B) vs placebo	DB, RCT Patients with chronic stable angina	N=206 4 weeks	Primary: Effectiveness in chronic stable angina (serial treadmill testing performed 0, four, eight and 12 hours after patch application at baseline and on days one, 15 and 29) Secondary: Adverse reaction	Primary: Improved walking times were observed in both Group A and Group B over placebo at all testing points after short-term administration. Results were statistically significant for Group A at 12 hours and for Group B at four, eight and 12 hours. At weeks two and four, walking times were again greater in Group B over placebo at all testing points with the four hour test time at week two and the eight hour test time at week two and four reaching statistical significance. Group A did not demonstrate increased duration in walking time long-term. Secondary: Active therapy was generally tolerated well. An increase in nonexertional angina during the patch-off interval was reported in nine patients.
Ninomiya et al.[25] (2008) ISDN ER 40 mg/day or ISMN ER 40 mg/day vs	RCT Patients suspected to have angina pectoris and with normal or mildly diseased coronary arteries underwent	N=42 Not specified	Primary: Coronary wall shear stress Secondary: Changes in coronary blood flow	Primary: The percent increase in coronary blood flow and coronary artery diameter induced by acetylcholine was significantly smaller in the ISDN/ISMN group than in the calcium channel blocker group (33±74 vs 83±77%; P<0.05, -3±16 vs 11±12%; P<0.01, respectively). Secondary: The percent diameter decrease in the region of greatest constrictive

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 5mg/day or nifedipine ER 20 mg/day	Doppler flow study of the left anterior descending coronary artery. All patients had been taking long acting nitrates or calcium channel blockers for ≥1 year			response to acetylcholine was significantly greater in the ISDN/ISMN group than in the calcium channel blocker group (44±39 vs 15±32%; P<0.02).
Unstable Angina				
Dellborg et al.[26] (1991) NTG IV for 24 hours vs NTG administered buccally every 4 hours	RCT Patients admitted to the coronary care unit due to UA	N=29 24 hours	Primary: Efficacy Secondary: Adverse effects	Primary: Efficacy was comparable in the two groups Secondary: Less adverse effects (headache, hemodynamic intolerance) were associated with buccal nitroglycerin than IV although the differences were not significant.
Kaplan et al.[27] (1983) NTG IV 10 µg/min increased by 10 µg/min every 5 minutes to 50 µg/min then increased by 50 µg/min per each episode of angina	OL, OS Patients with angina at rest unresponsive to standard therapy including oral or topical nitrates and β-blockers	N=35 24 hours	Primary: Clinical response Secondary: Not reported	Primary: NTG therapy reduced the number of episodes of angina at rest from 3.5±0.4 to 0.3±0.1, reduced doses of sublingual NTG from 1.9±0.3 to 0.4±0.1 mg/day and decreased morphine sulfate use from 5.5±1.3 to 0.4±0.2 mg/day (P<0.001 for all). Complete response, defined as no rest angina, was achieved in 25 patients, while eight patients experienced greater than a 50% reduction in episodes and two patients where nonresponders. Secondary: Not reported
Karlberg et al.[28] (1998) NTG IV titrated from 1.5 mL/hour	DB, PC, RCT Patients with recent onset of chest pain, suggestive of	N=143 48 hours	Primary: Reduction in ongoing signs of myocardial ischemia,	Primary: Treatment with NTG IV resulted in fewer patients (13) experiencing ongoing signs of ischemia (AP1 + AP2) than placebo (25; P<0.03). There were significantly less patients on active treatment that required >2 sublingual NTG tablets compared to placebo (12 vs 22; P<0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in <1 hour to a maximum of 12 mL/hour vs placebo	myocardial ischemia or worsening of previously stable angina pectoris and clinical evidence of underlying CAD		leukocyte activation, inhibition of platelet aggregation Secondary: Adverse effects	There was no significant difference found between groups in regards to leukocyte activation or inhibition of platelet aggregation. Secondary: Active treatment was stopped in seven patients compared to zero in the placebo group (P<0.001). Five patients terminated therapy prematurely because of headache while two patients stopped because of a decrease in BP and bradycardia.
Heart Failure				
Cohn et al.[29] (1986) V-HeFT I ISDN 160 mg/day and hydralazine 300 mg/day vs prazosin 20 mg/day vs placebo	AC, DB, PC, RCT Men with impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic	N=642 3 years	Primary: Mortality Secondary: Effect on left ventricular function	Primary: There was a 34% risk reduction in mortality by two years in the ISDN plus hydralazine group compared to placebo (P<0.028). Cumulative mortality rates of 25.6 and 36.2% were observed in the ISDN plus hydralazine group at two and three years respectively, compared to 34.3 and 46.9% in the placebo group. The results found in the prazosin group were similar to placebo. Secondary: A significant increase in the LVEF was reported at eight weeks and one year in the ISDN plus hydralazine treatment group, but not in either the prazosin or placebo groups.
Cohn et al.[30] (1991) ISDN 40 mg QID and hydralazine 75 mg QID (individual agents, concurrent therapy) vs	AC, DB, RCT Men with heart failure (primarily NYHA class II and III), receiving digoxin and diuretics	N=804 2 years	Primary: All-cause mortality Secondary: Not reported	Primary: The results demonstrated significantly lower mortality after two years with enalapril (18%) vs ISDN and hydralazine (25%; P=0.016). In addition, overall mortality tended to be lower with enalapril vs ISDN and hydralazine (P=0.08). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enalapril 10 mg BID				
Taylor et al.[31] (2004) A-HeFT ISDN 20 mg TID and hydralazine 37.5 mg TID, increased to ISDN 40 mg TID plus hydralazine 75 mg TID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for ≥3 months and evidence of left ventricular dysfunction within the prior 6 months	N=1,050 Mean duration of follow-up was 10 months	Primary: A composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, quality of life changes Secondary: Not reported	Primary: Combination of vasodilators in addition to standard therapy had significant mortality benefit (mortality rate of 6.2 vs 10.2%; P=0.02). From a range of possible scores of -6 to 2, patients in the active treatment group achieved a significantly better score of -0.1±1.9 compared to -0.5±2.0 in the placebo group (P=0.01). Each separate value of the composite score was also significantly better in the active group when compared to placebo. There was a 43% decrease in the rate of death from any cause (HR, 0.57; P=0.01), and a 33% reduction in the rate of first hospitalizations (P=0.001). This led to the early termination of the trial. Additionally, there was a significant improvement in quality of life scores found with ISDN plus hydralazine when compared to placebo (-5.6±20.6 vs -2.7±21.2; P=0.02). Secondary: Not reported
Taylor et al.[32] (2007) A-HeFT ISDN 20 mg TID and hydralazine 37.5 mg TID, increased to ISDN 40 mg TID and hydralazine 75 mg TID vs placebo	Post-hoc analysis of A-HeFT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for ≥3 months and evidence of left ventricular dysfunction within the prior 6 months	N=1,050 Mean duration of follow-up was 18 months	Primary: Cause specific mortality, event free survival (time to either death or first hospitalization and time to first hospitalization for heart failure Secondary: Subgroup analysis	Primary: Cardiovascular deaths were significantly reduced in the treatment group compared to the placebo group (5.0 vs 8.5%; P=0.027). Pump failure death was also significantly reduced (75%) compared to the placebo group (0.8 vs 3.0%; P=0.012). There were no significant differences between the groups for other causes of death. In the treatment group event-free survival (death or first hospitalization for heart failure) was significantly improved compared to the placebo group (HR, 0.63; 95% CI, 0.49 to 0.81; P<0.001). The time to first hospitalization for heart failure was also significantly reduced (HR, 0.61; 95% CI, 0.46 to 0.80; P<0.001). Secondary: A consistent beneficial effect was seen in the treatment sub groups (age,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sex, baseline BP, history of chronic renal insufficiency, presence of diabetes, cause of heart failure, and baseline medication use) on primary composite score and event-free survival.
Yancy et al.[33] (2007) X-A-HeFT ISDN 20 mg TID and hydralazine 20 mg TID, titrated up to ISDN 40 mg TID and hydralazine 75 mg TID vs placebo	ES, OL Patients previously enrolled in A-HeFT with NYHA class I to IV heart failure symptoms while receiving background therapy and satisfying the A-HeFT inclusion criteria	N=158 12 months or until ISDN-hydralazine approved by the FDA	Primary: Compliance with study drug, safety, tolerability Secondary: Change in NYHA association class, death, hospitalization for heart failure	Primary: Compliance in the treatment group averaged 87±25%, with no significant difference when compared to the placebo group. There were no significant differences in adverse events between the groups. Secondary: No significant difference was seen in hospitalizations from heart failure according to randomization. The greatest improvement in heart failure symptoms occurred in NYHA class III (at baseline) compared to other classes (P<0.001). Overall most patients were unchanged with 24% showing improved NYHA class and 9% showing a worsening.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, ISDN=isosorbide dinitrate, ISMN=isosorbide mononitrate, IV=intravenous, NTG=nitroglycerin, QID=four times daily, TID=three times daily
Study abbreviations: AC=active comparator, DB=double-blind, ES=extended study, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, XO=cross-over
Miscellaneous abbreviations: BP=blood pressure, CAD=coronary artery disease, DBP=diastolic blood pressure, FDA=Food and Drug Administration, HR=hazard ratio, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, SBP=systolic blood pressure, UA=unstable angina

Additional Evidence

Dose Simplification
Kardas et al evaluated adherence rates with once daily isosorbide mononitrate compared to twice daily isosorbide mononitrate over the course of 10 weeks. Adherence rates were significantly better with the once daily regimen compared to the twice daily regimen (P<0.001). The once daily regimen also led to a significant reduction in the mean weekly number of chest pain episodes compared to the twice-daily regimen (P<0.0001).[34] Brun et al evaluated adherence with a once daily and twice daily formulation of isosorbide mononitrate in patients with stable angina. Adherence rates were better with the once daily regimen compared to the twice daily regimen. The improvement in adherence also resulted in fewer angina episodes and a reduction in the number of nitroglycerin tablets that were taken to treat acute angina attacks.[35]

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 Nitrates and Nitrites

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Isosorbide dinitrate	tablet	Isordil®*, Isordil Titradose®*	$$$$	$$$$
Isosorbide mononitrate	extended-release tablet, tablet	N/A	N/A	$
Nitroglycerin	injection, ointment, sublingual powder, sublingual tablet, transdermal patch, translingual spray	GoNitro®, Nitro-Bid®, Nitro-Dur®*, Nitrolingual®*, Nitrostat®*	$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The nitrates and nitrites are approved for the acute, prophylactic, and chronic treatment of angina. In addition, intravenous nitroglycerin is approved for the control of congestive heart failure in the setting of myocardial infarction, for the induction of intraoperative hypotension, and for the treatment of perioperative hypertension.[2-9] All of the nitrate and nitrite agents are available in a generic formulation.

Several organizations provide recommendations on the use of the nitrates and nitrites. Sublingual nitroglycerin tablets and nitroglycerin spray are recommended for the immediate relief of angina in all patients. For the treatment of chronic angina, β-blockers are recommended as first-line therapy. Long-acting calcium channel blockers or long-acting nitrates may be used if initial therapy is not successful, or if β-blockers are contraindicated. Combination therapy may be necessary in certain patients. The combination of β-blockers and long-acting nitrates are preferred due to their efficacy and safety.[10,12] Sublingual and intravenous nitroglycerin are recommended for the acute treatment of unstable angina, myocardial infarction, and acute coronary syndrome in addition to standard therapy. For the treatment of heart failure, angiotensin converting enzyme (ACE) inhibitors, β-blockers, and diuretics are the cornerstones of therapy. The combination hydralazine and a nitrate is an alternative treatment option in patients with heart failure who have reduced left ventricular ejection function when ACE inhibitors or angiotensin II receptor blockers are not tolerated. Furthermore, the combination hydralazine and a nitrate is recommended to improve outcomes for patients self-described as African American who have moderate to severe symptoms on optimal therapy with ACE inhibitors, β-blockers, and diuretics. The addition of hydralazine and a nitrate is reasonable for patients with heart failure who are already taking an ACE inhibitor and β-blocker for symptomatic heart failure, but who have persistent symptoms.[10,12,15-17]

Since all nitrates have similar pharmacologic effects, product selection is based on the desired onset and duration of action. Tolerance develops after chronic exposure to nitrates, regardless of the route of administration or formulation used. This can be overcome by instituting short periods (10 to 12 hours) of withdrawal from nitrate therapy.[2-9]

There is insufficient evidence to support that one brand nitrate or nitrite 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 nitrates or nitrites 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 nitrate or nitrite 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of
Miscellaneous Renin-Angiotensin-Aldosterone System Inhibitors
AHFS Class 243292
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I. Overview

Heart failure (HF) is characterized by fluid retention and/or poor systemic perfusion that results from structural or functional impairment of ventricular filling or ejection of blood from the heart.[1] Treatment of symptomatic HF typically consists of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blocker (ARB) and a β-blocker to reduce morbidity and mortality. In the case of volume overload, a diuretic agent may be added on to therapy to improve symptoms.[1] The 2022 American Heart Association/American College of Cardiology/ Heart Failure Society of America guideline for the management of HF state that in patients with heart failure with reduced ejection fraction (HFrEF) and NYHA class II to III symptoms, the use of an angiotensin receptor/neprilysin inhibitor (ARNI) is recommended to reduce morbidity and mortality. In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible.[1]

Entresto® (sacubitril-valsartan) is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an ARB, that is Food and Drug Administration (FDA)-approved to reduce the risk of cardiovascular death and hospitalization for HF in adult patients with chronic heart failure. Benefits are most clearly evident in patients with LVEF below normal. It is also indicated for the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto® reduces NT-proBNP and is expected to improve cardiovascular outcomes. Entresto® is the first-in-class FDA-approved ARNI.[2] This agent provides cardiovascular and renal benefits through two distinct mechanisms. The first mechanism consists of the inhibition of neprilysin by LBQ657, the active metabolite of the prodrug sacubitril. Inhibition of neprilysin reduces the degradation of natriuretic peptides which promote natriuresis, diuresis, and vasodilation associated with inhibition of the renin-angiotensin-aldosterone and sympathetic nervous systems, as well as trophic effects that oppose cardiac hypertrophy and fibrosis. The second mechanism consists of the selective antagonism of the angiotensin II type-1 (AT1) receptor by valsartan. This blockade of the AT1 receptor inhibits the effects of angiotensin II, including angiotensin II-dependent aldosterone release.[2,3]

The miscellaneous renin-angiotensin-aldosterone system (RAAS) inhibitor products included in this review are listed in Table 1. Sacubitril-valsartan is not available in a generic formulation. This class was last reviewed in February 2022.

Table 1. Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Sacubitril and valsartan	tablet	Entresto®	Entresto®

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2.

Table 2. Treatment Guidelines for Using RAAS Inhibitors

Clinical Guideline	Recommendation(s)
American Heart Association/ American College of Cardiology/ Heart Failure Society	Treatment of Stage A heart failure (HF) • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations

Clinical Guideline	Recommendation(s)
of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)[1]**	for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u> • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C)

Clinical Guideline	Recommendation(s)
	• In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B)

Clinical Guideline	Recommendation(s)
	Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) Pharmacological treatment for Stage C HF with preserved EF (HFpEF) • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) Treatment of Stage D (advanced/refractory) HF • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as “bridge therapy” in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B) Treatment of Transthyretin Cardiac Amyloidosis • In select patients with wild-type or variant trans-thyretin cardiac amyloidosis and NYHA class I to III HF symptoms, transthyretin tetramer sta-bilizer therapy (tafamidis) is indicated to reduce cardiovascular morbidity and mortality. • At 2020 list prices, tafamidis provides low economic value (>$180 000 per QALY gained) in patients with HF with wild-type or variant transthyretin cardiac amyloidosis. • In patients with cardiac amyloidosis and AF, anticoagulation is reasonable to reduce the risk of stroke regardless of the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category) score.
European Society of Cardiology: **Guidelines for the**	Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a beta-blocker, for symptomatic

Clinical Guideline	Recommendation(s)
Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)[4]	patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a beta-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a beta-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.

Clinical Guideline	Recommendation(s)
	• A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk • of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
National Institute for Health and Clinical Excellence:	<u>Treating heart failure with reduced ejection fraction</u> • First-line treatment o Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker

Clinical Guideline	Recommendation(s)
Chronic heart failure in adults: management (2018)[5]	licensed for heart failure to people who have heart failure with reduced ejection fraction. • ACE inhibitors o Do not offer ACE inhibitor therapy if there is a clinical suspicion of hemodynamically significant valve disease until the valve disease has been assessed by a specialist. o Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every two weeks) until the target or maximum tolerated dose is reached. o Measure serum sodium and potassium, and assess renal function, before and one to two weeks after starting an ACE inhibitor, and after each dose increment. o Measure blood pressure before and after each dose increment of an ACE inhibitor. o Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell. • Alternative treatments if ACE inhibitors are not tolerated o Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side effects with ACE inhibitors. o Measure serum sodium and potassium, and assess renal function, before and after starting an ARB and after each dose increment. o Measure blood pressure after each dose increment of an ARB. o Once the target or maximum tolerated dose of an ARB is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell. o If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have heart failure with reduced ejection fraction. • Beta-blockers o Do not withhold treatment with a beta-blocker solely because of age or the presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. o Introduce beta-blockers in a 'start low, go slow' manner. Assess heart rate and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. o Switch people whose condition is stable and who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. • Mineralocorticoid receptor antagonists (MRAs) o Offer an MRA, in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. o Measure serum sodium and potassium, and assess renal function, before and after starting an MRA and after each dose increment. o Measure blood pressure before and after each dose increment of an MRA. o Once the target, or maximum tolerated, dose of an MRA is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell. • Specialist treatment o Ivabradine is recommended as an option for treating chronic heart failure for people: ▪ with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and

Clinical Guideline	Recommendation(s)
	▪ who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and ▪ who are given ivabradine in combination with standard therapy including beta-blocker therapy, ACE inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and ▪ with a left ventricular ejection fraction of 35% or less. o Ivabradine should only be initiated after a stabilization period of four weeks on optimized standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. o Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. o Sacubitril-valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: ▪ with New York Heart Association (NYHA) class II to IV symptoms and ▪ with a left ventricular ejection fraction of 35% or less and ▪ who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or ARBs. o Treatment with sacubitril-valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. o Hydralazine in combination with nitrate ▪ Seek specialist advice and consider offering hydralazine in combination with nitrate (especially if the person is of African or Caribbean family origin and has moderate to severe heart failure [NYHA class III/IV] with reduced ejection fraction). o Digoxin ▪ Digoxin is recommended for worsening or severe heart failure with reduced ejection fraction despite first-line treatment for heart failure. Seek specialist advice before initiating. ▪ Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within eight to 12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence. ▪ The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. <u>Treating heart failure with reduced ejection fraction in people with chronic kidney disease</u> • For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR of 30 ml/min/1.73 m^2 or above: o offer the treatment outlined above and o if the person's eGFR is 45 ml/min/1.73 m^2 or below, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, MRAs and digoxin. • For people who have heart failure with reduced ejection fraction and chronic kidney disease with an eGFR below 30 ml/min/1.73 m^2, the specialist heart failure multidisciplinary team should consider liaising with a renal physician. • Monitor the response to titration of medicines closely in people who have heart failure with reduced ejection fraction and chronic kidney disease, taking into account the increased risk of hyperkalemia. <u>Managing all types of heart failure: Pharmacological treatment</u>

Clinical Guideline	Recommendation(s)

	• Diuretics
	  ○ Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies.
	  ○ People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice.
	• Calcium-channel blockers
	  ○ Avoid verapamil, diltiazem and short-acting dihydropyridine agents in people who have heart failure with reduced ejection fraction.
	• Amiodarone
	  ○ Make the decision to prescribe amiodarone in consultation with a specialist.
	  ○ Review the need to continue the amiodarone prescription at the six-monthly clinical review.
	  ○ Offer people taking amiodarone liver and thyroid function tests, and a review of side effects, as part of their routine 6-monthly clinical review.
	• Anticoagulants
	  ○ For people who have heart failure and atrial fibrillation, follow the recommendations on anticoagulation in the NICE guideline on atrial fibrillation. Be aware of the effects of impaired renal and liver function on anticoagulant therapies.
	  ○ In people with heart failure in sinus rhythm, anticoagulation should be considered for those with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus.
	• Vaccinations
	  ○ Offer people with heart failure an annual vaccination against influenza.
	  ○ Offer people with heart failure vaccination against pneumococcal disease (only required once).
	• Contraception and pregnancy
	  ○ In women of childbearing potential who have heart failure, contraception and pregnancy should be discussed. If pregnancy is being considered or occurs, specialist advice should be sought. Subsequently, specialist care should be shared between the cardiologist and obstetrician.

ACEI=angiotensin-converting enzyme inhibitor, ACS=acute coronary syndrome, AF=atrial fibrillation, ARB=angiotensin-receptor blocker, CAD=coronary artery disease, EF=ejection fraction, GDMT=guideline-directed medical therapy, HF=heart failure, HFrEF=heart failure with reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction, LV=left ventricular, LVEF=left ventricular ejection fraction, MI= myocardial infarction, NSAIDS=non-steroidal antiinflammatory drugs, NYHA=New York Heart Association

III. Indications

The FDA-approved indications for miscellaneous RAAS inhibitors are noted in Table 3.

Table 3. FDA-Approved Indications for Miscellaneous RAAS Inhibitors[2]

Indication	Sacubitril-valsartan
Reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic HF. Benefits are most clearly evident in patients with left ventricular ejection fraction below normal.	✔
Treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes.	✔

HF=heart failure

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous RAAS inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters for Miscellaneous RAAS Inhibitors[2]

Generic Name(s)	Bioavailability	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Sacubitril-valsartan	Sacubitril: ≥60 Valsartan: Not reported*	94 to 97	Converted by esterases to LBQ657 (sacubitril)/minimally metabolized (valsartan)	Renal: 52 to 68 (sacubitril)/~13 (valsartan) Fecal: 37 to 48 (sacubitril)/86 (valsartan)	Sacubitril: 1.4 Valsartan: 9.9 LBQ657: 11.5

* The valsartan component in Entresto® is more bioavailable than the valsartan in other marketed tablet formulations.

V. Drug Interactions

Major drug interactions with miscellaneous RAAS inhibitors are listed in Table 5.

Table 5. Major Drug Interactions with Miscellaneous RAAS Inhibitors[2,6]

Generic Name(s)	Interaction	Mechanism
ARB	Aliskiren	Direct renin inhibitor and ARB may have additive effects on the renin-angiotensin-aldosterone system. Concomitant use of aliskiren and an ARB, such as valsartan, is contraindicated in patients with diabetes due to increased risk of hyperkalemia, hypotension, and renal impairment. The combination of aliskiren with valsartan should also be avoided in patients with renal impairment (GFR < 60 mL/min).
Sacubitril-valsartan	ACEI	Dual blockade of the renin-angiotensin-aldosterone system by concomitant use of an ACEI and an ARB may increase the risk of adverse events, including angioedema, hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure).
ARB	Lithium	Concomitant use of lithium and an ARB may increase the risk of lithium toxicity.
OATP1B1/3 substrates	Simeprevir	Simeprevir inhibits OATP1B1/3-mediated efflux transport. Concomitant use of simeprevir and an OATP1B1/3 substrate may result in increased exposure to the OATP1B1/3 substrate.
Potassium-sparing agents	Trimethoprim	Trimethoprim and other potassium-sparing agents may have additive effects on serum potassium. Concomitant use of trimethoprim with drugs known to induce hyperkalemia, including ARBs, may result in increased risk of hyperkalemia.

ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, GFR=glomerular filtration rate, OATP=organic anion transporting polypeptide

VI. Adverse Drug Events

The most common adverse drug events reported with miscellaneous RAAS inhibitors are listed in Table 6. The boxed warning for sacubitril-valsartan is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with Miscellaneous RAAS Inhibitors[2,6]

Adverse Event	Sacubitril-valsartan
Angioedema	0.5*
Cough	9.0

Adverse Event	Sacubitril-valsartan
Decrease in hemoglobin/hematocrit >20%	5.0
Dizziness	6.0
Falls	1.9
Hyperkalemia	12.0
Hypotension	18.0
Increase in serum creatinine >50%	16.0
Orthostasis	2.1
Renal failure/acute renal failure	5.0
Serum potassium >5.5 mEq/L	16.0

ˇ Percent not specified.
- Event not reported.
* The rate of angioedema in the Black population was 2.4%

Table 7. Boxed Warning for sacubitril-valsartan[2]

WARNING
WARNING: FETAL TOXICITY • When pregnancy is detected, discontinue sacubitril-valsartan as soon as possible. • Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

VII. Dosing and Administration

The usual dosing regimens for miscellaneous RAAS inhibitors are listed in Table 8.

Table 8. Usual Dosing Regimens for Miscellaneous RAAS Inhibitors[2]

<table>
<tr><th>Generic Name</th><th>Usual Adult Dose*</th><th>Usual Pediatric Dose</th><th>Availability</th></tr>
<tr><td>Sacubitril-valsartan</td><td><u>Heart failure:</u>
Tablet: initial, 49/51 mg BID; maintenance and maximum, 97/103 mg BID</td><td><u>Pediatric heart failure in patients aged one year and older:</u>
Tablet: Take the recommended dose BID and adjust dose every two weeks as tolerated by the patient:
<table>
<tr><td></td><td>Starting</td><td>Second</td><td>Final</td></tr>
<tr><td><40 kg</td><td>1.6 mg/kg</td><td>2.3 mg/kg</td><td>3.1 mg/kg</td></tr>
<tr><td>40 to <50 mg</td><td>24/26 mg</td><td>49/51 mg</td><td>72/78 mg</td></tr>
<tr><td>≥50 kg</td><td>49/51 mg</td><td>72/78 mg</td><td>97/103 mg</td></tr>
</table></td><td>Tablets:
24 mg/26 mg
49 mg/51 mg
97 mg/103 mg</td></tr>
</table>

ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, NYHA=New York Heart Association
Drug regimen abbreviations: BID=twice daily
* If switching from an ACE inhibitor to sacubitril-valsartan allow a 36-hour washout period between the two drugs; see package insert for dose adjustments for patients not taking an ACE inhibitor or ARB or previously taking low doses of these agents, severe renal impairment, and hepatic impairment.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of miscellaneous RAAS inhibitors are summarized in Table 9.

Table 9. Comparative Clinical Trials with Miscellaneous RAAS Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
McMurray et al.[7,8] (2014) PARADIGM-HF Sacubitril-valsartan (LCZ696) 200 mg BID vs enalapril 10 mg BID After discontinuing their existing ACEI/ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily for two weeks then held therapy with enalapril for one day, followed by sacubitril-valsartan 100 mg twice-daily, increasing to 200 mg twice daily for four to six weeks before being randomized in final	AC, DB, MC, PG, RCT Adults with chronic HF (NYHA Class II to IV) symptoms, an LVEF of ≤40% (changed to ≤35% later in study) and a BNP ≥150 pg/mL (or N terminal proBNP ≥600 pg/mL), or, if hospitalized for HF within previous 12 months, a BNP of ≥100 pg/mL (or NT-proBNP ≥400 pg/mL), stable dose of a β-blocker (unless contraindicated or not tolerated), and a ACE-I or ARB equivalent to enalapril 10 mg daily for at least four weeks before screening along with a mineralocorticoid antagonist (if	N=8,399 Median follow-up of 27 months (study terminated by data safety and monitoring board due to the boundary for an over-whelming benefit with sacubitril-valsartan had been reached)	Primary: Composite of death from cardiovascular causes or a first hospitalization for heart failure Secondary: Time to death from any cause, the change from baseline to eight months in the clinical summary score on the KCCQ, time to new onset AF, and time to first occurrence of decline in renal function (defined as ESRD, a decrease in eGFR of ≥50%, or a decrease of ≥30 mL/min/1.73 m^2)	Primary: Sacubitril-valsartan was associated with a greater risk reduction of the combined cardiovascular endpoint compared to enalapril (914 [21.8%] vs 1,117 [26.5%]; HR, 0.80; 95% CI, 0.73 to 0.87; P=0.0000004). This treatment effect reflected a greater reduction in risk of cardiovascular death (558 [13.3%] vs 693 [16.5%]; HR, 0.80; 95% CI, 0.71 to 0.89; P<0.001) and HF hospitalization (537 [12.8%] vs 658 [15.6%]; HR, 0.79; 95% CI, 0.71 to 0.89; P<0.001) with sacubitril-valsartan compared to enalapril. The NNT for the composite primary endpoint and for cardiovascular death were 21 and 32, respectively. Secondary: Sacubitril-valsartan was associated with a reduction in all-cause mortality compared to enalapril (711 [17.0%] vs 835 [19.8%]; HR, 0.84; 95% CI, 0.76 to 0.93; P <0.0001). The mean change from baseline to month eight in the KCCQ clinical summary score was a reduction in 2.99 points in the sacubitril-valsartan group and a reduction of 4.63 points in the enalapril group (between group difference, 1.64 points; 95% CI, 0.63 to 2.65; P=0.001). New onset atrial fibrillation was comparable for both groups (84 patients in the sacubitril-valsartan group and 83 in the enalapril group, P=0.84). Protocol-defined decline in renal function was seen in 94 patients in the sacubitril-valsartan group compared to 108 patients in the enalapril group (P=0.28). Among these patients, progression to ESRD was seen in eight patients in the sacubitril-valsartan group compared to 16 patients in the enalapril group (P=0.11).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
phase to sacubitril-valsartan or enalapril.	indicated)			
Mogensen et al.[9] (2017) PARADIGM-HF Sacubitril-valsartan 200 mg BID vs enalapril 10 mg BID After discontinuing their existing ACEI/ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily for two weeks then held therapy with enalapril for one day, followed by sacubitril-valsartan 100 mg twice-daily, increasing to 200 mg twice daily for four to six weeks before being randomized in final phase to sacubitril-valsartan or enalapril.	AC, DB, MC, PG, RCT Adults with chronic HF (NYHA Class II to IV) symptoms, an LVEF of ≤40% (changed to ≤35% later in study) and a BNP ≥150 pg/mL (or N terminal proBNP ≥600 pg/mL), or, if hospitalized for HF within previous 12 months, a BNP of ≥100 pg/mL (or NT-proBNP ≥400 pg/mL), stable dose of a β-blocker (unless contraindicated or not tolerated), and a ACE-I or ARB equivalent to enalapril 10 mg daily for at least four weeks before screening along with a mineralocorticoid antagonist (if indicated)	N=8,399 Median follow-up of 27 months (study terminated by data safety and monitoring board due to the boundary for an over-whelming benefit with sacubitril-valsartan had been reached)	Primary: Composite of CV death or HF hospitalization Secondary: Composite of CV death, HF hospitalization, MI, stroke, and resuscitated sudden death; coronary composite outcome of CV death, non-fatal MI, hospitalization for unstable angina pectoris, hospitalization for "other" angina, or coronary revascularization	Primary: Sacubitril-valsartan was associated with a reduction in the primary composite endpoint compared to enalapril (HR, 0.80; 95% CI, 0.73 to 0.87; P<0.001). Secondary: Sacubitril-valsartan was associated with a reduction in the secondary composite endpoint compared to enalapril (HR, 0.83; 95% CI, 0.76 to 0.90; P<0.001). Sacubitril-valsartan was associated with a reduction in the coronary composite endpoint compared to enalapril (HR, 0.83; 95% CI, 0.75 to 0.92; P<0.001). Although each of the components of the coronary composite occurred less frequently in the sacubitril-valsartan group, compared with the enalapril group, only CV death was reduced significantly.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Solomon et al.[10] (2019) PARAGON-HF Sacubitril-valsartan 200 mg BID vs valsartan 160 mg BID	DB, MC, RCT Patients ≥50 years of age with signs and symptoms of HF, NYHA class II to IV, an ejection fraction ≥45% within the previous 6 months, elevated level of natriuretic peptides, evidence of structural heart disease, and diuretic therapy	N=4,822	Primary: Composite of total hospitalizations for HF and death from CV causes Secondary: NYHA class change, worsening renal function, and change in KCCQ clinical summary score (scale, 0 to 100, with higher scores indicating fewer symptoms and physical limitations), safety	Primary: There were 894 primary events (690 hospitalizations for HF and 204 deaths from CV causes) in 526 patients in the sacubitril–valsartan group and 1009 primary events (797 hospitalizations for HF and 212 deaths from CV causes) in 557 patients in the valsartan group (rate ratio, 0.87; 95% CI, 0.75 to 1.01; P=0.06). Because this difference did not meet the predetermined level of statistical significance, subsequent analyses were considered to be exploratory. Secondary: The incidence of death from CV causes was 8.5% in the sacubitril-valsartan group and 8.9% in the valsartan group (HR, 0.95; 95% CI, 0.79 to 1.16); there were 690 and 797 total hospitalizations for HF, respectively (rate ratio, 0.85; 95% CI, 0.72 to 1.00). NYHA class improved in 15.0% of the patients in the sacubitril-valsartan group and in 12.6% of those in the valsartan group (odds ratio, 1.45; 95% CI, 1.13 to 1.86); renal function worsened in 1.4% and 2.7%, respectively (HR, 0.50; 95% CI, 0.33 to 0.77). The mean change in the KCCQ clinical summary score at eight months was 1.0 point (95% CI, 0.0 to 2.1) higher in the sacubitril-valsartan group. Patients in the sacubitril-valsartan group had a higher incidence of hypotension and angioedema and a lower incidence of hyperkalemia.
Velazquez et al.[11] (2019) PIONEER-HF Sacubitril-valsartan 200 mg BID vs enalapril 10 mg BID	DB, MC, RCT Patients ≥18 years of age with heart failure with reduced ejection fraction who were hospitalized for acute decompensated heart failure	N=881 8 weeks	Primary: Time-averaged proportional change in the NT-proBNP concentration from baseline through weeks four and eight Secondary: Rates of worsening renal function, hyperkalemia, symptomatic	Primary: The NT-proBNP concentration decreased in both treatment groups. The time-averaged reduction in the NT-proBNP concentration was greater in the sacubitril–valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks four and eight to the baseline value was 0.53 in the sacubitril–valsartan group as compared with 0.75 in the enalapril group (percent change, −46.7% vs −25.3%; ratio of change with sacubitril–valsartan vs enalapril, 0.71; 95% CI, 0.63 to 0.81; P<0.001). Secondary: The rates of worsening renal function, hyperkalemia, and symptomatic hypotension did not differ significantly between the sacubitril–valsartan group and the enalapril group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hypotension, and angioedema	
Mann et al.[12] (2022) LIFE Sacubitril/valsartan, 97/103 mg (200-mg fixed dose), twice daily vs valsartan, 160 mg, twice daily	DB, DD, MC, PRO, RCT Patients with advanced chronic heart failure with a reduced ejection fraction and recent NYHA class IV symptoms	N=335 24 weeks	Primary: AUC of NT-proBNP levels compared to baseline Secondary: Number of days the patient was alive, out of the hospital, and free from any of the following outcomes: listing for cardiac transplant, cardiac transplant, implantation of a left ventricular assist device, receipt of continuous inotropic therapy for seven or more days, or hospitalization for HF on two or more occasions other than the index admission; tolerability	Primary: Compared with baseline levels, the median AUC for NT-proBNP was 1.08 (IQR, 0.75 to 1.60) for the sacubitril/valsartan treatment arm and 1.19 (IQR, 0.91 to 1.64) for the valsartan treatment arm. The estimated ratio of change for the AUC (primary end point) for sacubitril/valsartan vs valsartan was 0.95 (95% CI, 0.84 to 1.08; P=0.45). There were no informative differences in the AUC for NT-proBNP levels for sacubitril/valsartan compared with valsartan in any of the subgroups that were examined. Secondary: The secondary efficacy end point of the number of patient-days alive, out of hospital, and without heart failure events was numerically higher in the valsartan arm (median, 157.0; IQR, 53.5 to 164.0 days) compared with the sacubitril/valsartan arm (median, 147.0; IQR, 9.0 to 164.0 days). The estimated difference between the two groups was −11.2 days (95% CI, −26.4 to 4.0 days; P=0.15). There were no differences with respect to the development of symptomatic hypotension or worsening kidney function between the treatment arms, whereas significantly more patients developed hyperkalemia in the sacubitril/valsartan arm (28 [17%]) compared with the valsartan arm (15 [9%]) (P=0.04). Furthermore, there were no informative differences in other tolerability or serious adverse events between the treatment arms. The number of patients who discontinued the study drug in the sacubitril/valsartan arm compared with the valsartan treatment arm was not significantly different (hazard ratio, 1.36; 95% CI, 0.88 to 2.09; P=0.16).

Drug regimen abbreviations: BID=twice daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, HR=hazard ratio, MC=multicenter, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: ACEI=angiotensin converting enzyme inhibitor, AF=atrial fibrillation, ARB=angiotensin receptor blocker, AUC=area under the curve, BNP= B-type natriuretic peptide, CV=cardiovascular, ED=emergency department, ESRD=end-stage renal disease, eGFR=estimated glomerular filtration rate, GMP=guanosine monophosphate, HF=heart failure, KCCQ=Kansas City Cardiomyopathy Questionnaire, LVEF=left ventricular ejection fraction, NNT=number needed-to-treat, NT-proBNP=N-terminal pro-B-type natriuretic peptide, NYHA=New York Heart Association

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 Miscellaneous RAAS Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Sacubitril-valsartan	tablet	Entresto®	$$$$$	N/A

N/A=Not available

X. Conclusions

Entresto® (sacubitril-valsartan) is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an ARB, that is Food and Drug Administration (FDA)-approved to reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic HF. Benefits are most clearly evident in patients with left ventricular ejection fraction below normal. It is also indicated for the treatment of symptomatic heart failure (HF) with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.[2] It is the only agent currently available that targets both the natriuretic peptide and the renin-angiotensin-aldosterone system (RAAS). In the phase III PARADIGM-HF trial, this agent was shown to significantly reduce the rate of cardiovascular death, HF hospitalizations, and all-cause mortality compared to enalapril.[7-9]

Treatment of symptomatic HF typically consists of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blocker (ARB) and a β-blocker to reduce morbidity and mortality. In the case of volume overload, a diuretic agent may be added on to therapy to improve symptoms. The 2022 American Heart Association/American College of Cardiology/ Heart Failure Society of America guideline for the management of

HF state that in patients with heart failure with reduced ejection fraction (HFrEF) and NYHA class II to III symptoms, the use of an angiotensin receptor/neprilysin inhibitor (ARNI) is recommended to reduce morbidity and mortality. In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. Additionally, in patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.[1]

There is insufficient evidence to support that one brand miscellaneous renin-angiotensin-aldosterone system inhibitor 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 miscellaneous renin-angiotensin-aldosterone system inhibitors within the class reviewed are comparable to each other and to the generic products in the class (if applicable). Sacubitril-valsartan should be available as a first-line agent for patients with heart failure with reduced ejection fraction and NYHA class II to III.

XI. Recommendations

No brand miscellaneous renin-angiotensin-aldosterone system 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antidepressants
AHFS Class 281604
February 7, 2024

I. Overview

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa), and premenstrual dysphoric disorder.[1-3] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder, and unspecified anxiety disorder.[4] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis, and tobacco abuse.[1-3]

The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs), and miscellaneous agents. The agents which make up these subclasses differ with respect to their Food and drug Administration (FDA)-approved indications, mechanism of action, pharmacokinetics, adverse events, and drug interactions.

Monoamine oxidase is an enzyme that is distributed in various tissues throughout the body. This enzyme is responsible for the catabolism of monoamines ingested in food, as well as for the inactivation of neurotransmitters (e.g., serotonin, norepinephrine, and dopamine).[1,2] MAOIs increase the concentration of these neurotransmitters, which leads to their antidepressant activity. There are two types of monoamine oxidase, including MAO-A and MAO-B. The MAOIs differ with regards to selectivity for MAO receptor type and reversibility.[3] The SNRIs are potent inhibitors of neuronal norepinephrine and serotonin reuptake.[1-3] The SSRIs inhibit the neuronal uptake of serotonin and have minimal effects on norepinephrine or dopamine neuronal uptake.[1-3] The clinical efficacy of the SNRIs and SSRIs is thought to be related to the potentiation of neurotransmitter activity in the central nervous system. The exact mechanism of action of the serotonin modulators is unknown. Nefazodone inhibits neuronal uptake of serotonin and norepinephrine, and is a direct antagonist of serotonin ($5\text{-}HT_2$) receptors. Nefazodone and trazodone also block $alpha_1$-adrenergic receptors, which may be associated with postural hypotension.[1-3] Trazodone is thought to selectively inhibit serotonin uptake at the presynaptic neuronal membrane.[1,2] Vilazodone is a SSRI and partial serotonin $5\text{-}HT_{1A}$ receptor agonist.[3] Vortioxetine exhibits various serotonergic activities including the inhibition of the reuptake of serotonin, antagonistic effects at the $5\text{-}HT_3$, $5\text{-}HT_7$, and $5\text{-}HT_{1D}$ receptors, inhibition of the serotonin transporter, agonistic effects at $5\text{-}HT_{1A}$ receptors, and partial agonistic effects at $5\text{-}HT_{1B}$ receptors.[3] The TCAs interact with a wide variety of central nervous system receptor types, and as a result, cause many undesirable side effects. Clinically, they inhibit the reuptake of norepinephrine (secondary amines) and serotonin (tertiary amines) at the presynaptic neuron.[1-3] The miscellaneous antidepressants include brexanolone, bupropion, dextromethorphan-bupropion, esketamine, and mirtazapine. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine; it does not inhibit monoamine oxidase or the reuptake of serotonin.[3] Mirtazapine is a tetracyclic compound, but is unrelated to the TCAs. It acts as an antagonist at central $alpha_2$-adrenergic receptors, which is thought to result in an increase in central noradrenergic and serotonergic activity.[3] Mirtazapine is also a potent antagonist of histamine receptors and is a moderate peripheral $alpha_1$-adrenergic receptor antagonist, which results in sedation and orthostatic hypotension.[3] Brexanolone is a neuroactive steroid gamma-aminobutyric acid-A receptor positive modulator that is chemically identical to endogenous allopregnanolone, which is a potent neuroactive steroid that rises with progesterone levels during pregnancy. Brexanolone is indicated for the treatment of postpartum depression in patients 15 years of age and older and is administered intravenously.[3] Esketamine nasal spray is indicated in conjunction with an oral antidepressant for the treatment of adults with treatment-resistant depression or depressive symptoms with major depressive disorder with acute suicidal ideation or behavior. Esketamine is the S-enantiomer of racemic ketamine, and a non-selective, noncompetitive antagonist of the N-methyl-D-aspartate receptor. The precise mechanism of action of esketamine in major depressive disorder is unknown.[3] Dextromethorphan-bupropion is a combination of

dextromethorphan, an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, and bupropion. The exact mechanism of dextromethorphan in the treatment of major depressive disorder is unclear.[3]

The antidepressants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of the products are available in a generic formulation, and there is at least one generic product available in each antidepressant subclass. This class was last reviewed in February 2022.

Table 1. Antidepressants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Monoamine Oxidase Inhibitors			
Isocarboxazid	tablet	Marplan®	none
Phenelzine	tablet	Nardil®*	phenelzine
Selegiline	transdermal patch	Emsam®	none
Tranylcypromine	tablet	N/A	tranylcypromine
Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
Desvenlafaxine	extended-release tablet	Pristiq®*	desvenlafaxine
Duloxetine	delayed-release capsule	Cymbalta®*, Drizalma Sprinkle®	duloxetine
Levomilnacipran	extended-release capsule	Fetzima®	none
Venlafaxine	extended-release capsule, extended-release tablet, tablet	Effexor XR®*	venlafaxine
Selective Serotonin-reuptake Inhibitors			
Citalopram	capsule, solution, tablet	Celexa®*	citalopram
Escitalopram	solution, tablet	Lexapro®*	escitalopram
Fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*	fluoxetine
Fluvoxamine	extended-release capsule, tablet	N/A	fluvoxamine
Paroxetine	capsule, extended-release tablet, suspension, tablet	Paxil®*, Paxil CR®*, Pexeva®	paroxetine
Sertraline	capsule, oral concentrate, tablet	Zoloft®*	sertraline
Serotonin Modulators			
Nefazodone	tablet	N/A	nefazodone
Trazodone	tablet	N/A	trazodone
Vilazodone	tablet	Viibryd®*	vilazodone
Vortioxetine	tablet	Trintellix®	none
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents			
Amitriptyline	tablet	N/A	amitriptyline
Amoxapine	tablet	N/A	amoxapine
Clomipramine	capsule	Anafranil®*	clomipramine
Desipramine	tablet	Norpramin®*	desipramine
Doxepin	capsule, oral concentrate, tablet	Silenor®*	doxepin
Imipramine	capsule, tablet	N/A	imipramine
Nortriptyline	capsule, solution	Pamelor®*	nortriptyline
Protriptyline	tablet	N/A	protriptyline
Trimipramine	capsule	N/A	trimipramine
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products			
Amitriptyline and chlordiazepoxide	tablet	N/A	amitriptyline and chlordiazepoxide
Antidepressants, Miscellaneous			
Brexanolone	injection^	Zulresso®	none
Bupropion	extended-release tablet,	Aplenzin®, Forfivo XL®*,	bupropion

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	sustained-release tablet, tablet	Wellbutrin SR®*, Wellbutrin XL®*	
Dextromethorphan and Bupropion	extended-release tablet	Auvelity ER®	none
Esketamine	nasal spray	Spravato®	none
Mirtazapine	orally disintegrating tablet, tablet	Remeron®*	mirtazapine

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List.
N/A=Not available.

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Antidepressants

Clinical Guideline	Recommendation(s)
Department of Veterans Affairs and the Department of Defense: **Clinical Practice Guideline for the Management of Major Depressive Disorder (2022)**[5]	Treatment of Uncomplicated major depressive disorder (MDD) • We recommend that MDD be treated with either psychotherapy or pharmacotherapy as monotherapy, based on patient preference. Factors including treatment response, severity, and chronicity may lead to other treatment strategies such as augmentation, combination treatment, switching of treatments, or use of non-first line treatments. • When choosing psychotherapy to treat MDD, we suggest offering one of the following interventions (not rank ordered): o Acceptance and commitment therapy o Behavioral therapy/behavioral activation o Cognitive behavioral therapy o Interpersonal therapy o Mindfulness-based cognitive therapy o Problem-solving therapy o Short-term psychodynamic psychotherapy • For patients s who select psychotherapy as a treatment option, we suggest offering individual or group format based on patient preference. • There is insufficient evidence to recommend for or against combining components from different psychotherapy approaches. • For patients with mild to moderate MDD, we suggest offering clinician-guided computer/internet-based cognitive behavioral therapy either as an adjunct to pharmacotherapy or as a first-line treatment, based on patient preference. • When choosing an initial pharmacotherapy, or for patients who have previously responded well to pharmacotherapy, we suggest offering one of the following (not rank ordered): o Bupropion o Mirtazapine o A serotonin-norepinephrine reuptake inhibitor o Trazodone, vilazodone, or vortioxetine o A selective serotonin reuptake inhibitor • When choosing an initial pharmacotherapy, we suggest **against** using: o Esketamine o Ketamine o Monoamine oxidase inhibitors o Nefazodone o Tricyclic antidepressants

Clinical Guideline	Recommendation(s)
	• There is insufficient evidence to recommend for or against pharmacogenetic testing to help guide the selection of antidepressants. • For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies (either in-person or virtually), we suggest considering non-directive supportive therapy. Treatment of MDD that is Severe or has a Partial or Limited Response to Initial Treatment • We suggest offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD characterized as: o Severe (e.g., PHQ-9 >20) o Persistent major depressive disorder (duration greater than two years) o Recurrent (with two or more episodes) • For patients with MDD who have demonstrated partial or no response to an adequate trial of initial pharmacotherapy, we suggest (not rank ordered): o Switching to another antidepressant (including TCAs, MAOIs, or those in Recommendation 12) o Switching to psychotherapy o Augmenting with a psychotherapy o Augmenting with a second-generation antipsychotic • For patients who have demonstrated partial or no response to two or more adequate pharmacologic treatment trials, we suggest offering repetitive transcranial magnetic stimulation for treatment. • There is insufficient evidence to recommend for or against theta-burst stimulation for the treatment of MDD. • For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine as an option for augmentation. • We recommend offering electroconvulsive therapy (ECT) with or without psychotherapy for patients with severe MDD and any of the following conditions: o Catatonia o Psychotic depression o Severe suicidality o A history of a good response to ECT o Need for rapid, definitive treatment response on either medical or psychiatric grounds o The risks associated with other treatments are greater than the risks of ECT for this specific patient (i.e., co-occurring medical conditions make ECT the safest MDD treatment alternative) o A history of a poor response or intolerable side effects to multiple antidepressants
National Institute for Health and Clinical Excellence: **Depression in Adults: treatment and management (2022)**[6]	Chronic depressive symptoms • For people who present with chronic depressive symptoms that significantly impair personal and social functioning and who have not received previous treatment for depression, treatment options include cognitive behavioral treatment, SSRI, SNRI, TCA or combination therapy with CBT and either an SSRI or a TCA. • If a person with chronic depressive symptoms that significantly impair personal and social functioning cannot tolerate a particular SSRI, consider treatment with an alternative SSRI. • For people with chronic depressive symptoms that significantly impair personal

Clinical Guideline	Recommendation(s)
	and social functioning, who have not responded to SSRIs or SNRIs, consider alternative medication in specialist settings, or after consulting a specialist. Take into account that switching medication may mean that an adequate wash-out period is needed, particularly when switching to or from irreversible MAOIs or moclobemide. Alternatives include TCAs, moclobemide, irreversible MAOIs such as phenelzine, and low dose amisulpride. Further-line treatment • If a person's depression has not responded at all after four weeks of antidepressant medication at a recognized therapeutic dose, or after four to six weeks for psychological therapy or combined medication and psychological therapy, discuss with them whether there are any personal, social or environmental factors or physical or other mental health conditions that might explain why the treatment is not working and whether they have had problems adhering to the treatment plan. • If a person's depression has had no or a limited response to treatment with psychological therapy alone, and no obvious cause can be found and resolved, discuss further treatment options with the person including switching to an alternative psychological treatment including adding an SSRI to the psychological therapy and switching to an SSRI alone. • Only consider vortioxetine when there has been no or limited response to at least two previous antidepressants. • If a person with depression wants to try a combination treatment and is willing to accept the possibility of an increased side-effect burden, treatment options include adding an additional antidepressant medication from a different class, combining an antidepressant medication with a second-generation antipsychotic, or augmenting antidepressants with electroconvulsive therapy.

National Institute for Health and Care Excellence: **Antenatal and Postnatal Mental Health: Clinical Management and Service Guidance (2014)**[7]
 	
Last Updated February 2020
	Interventions for Depression
	• Consider facilitated self-help for pregnant or postnatal women with persistent subthreshold depressive symptoms, or mild to moderate depression.
	• Consider a TCA, SSRI, or SNRI for women with a history of severe depression who initially presented with mild depression in pregnancy or the postnatal period.
	• For women with moderate or severe depression in pregnancy or the postanal period consider:
	  ○ A high-intensity psychological intervention (i.e., CBT)
	  ○ TCA, SSRI or SNRI if the patient has expressed a preference for medication, declines psychological interventions, or has symptoms which have not responses to psychological interventions, or
	  ○ A high-intensity psychological intervention in combination with medication following no response, or limited response, to a high-intensity psychological intervention or medication alone
	• Consider gradually stopping the medication and facilitating therapy in women using a TCA, SSRI, or SNRI for mild/moderate depression who become pregnant.
	• In pregnant women taking a TCA, SSRI, or SNRI for severe depression, evaluate any previous response to treatment, stage of pregnancy, risk of relapse, risk associated with the patient's preferred therapies, and consider:
	  ○ Continuing the current medication
	  ○ Changing medications if there is an effective drug with a lower risk of adverse effects
	  ○ Combining the medication with a psychological intervention (e.g., CBT); or
	  ○ Switching to a high-intensity psychological intervention.

Clinical Guideline	Recommendation(s)

National Institute for Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder in Adults: management (2011)**[8]
 	
Last updated June 2020
	<u>Stepped care for people with generalized anxiety disorder (GAD)</u>
	• If a person with GAD chooses drug treatment, offer a SSRI, specifically sertraline.
	• If sertraline is ineffective, offer an alternative SSRI or a SNRI, taking into account the following factors:
	  ○ Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine).
	  ○ The side-effect profile and the potential for drug interactions.
	  ○ The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).
	  ○ The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference).
	• If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin.
	• Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.
	• Do not offer an antipsychotic for the treatment of GAD in primary care.
	
	<u>Panic disorder general considerations</u>
	• Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.
	• Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  ○ Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation).
	  ○ Pharmacological therapy (antidepressant therapy).
	  ○ Self-help interventions (i.e., bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface).
	• Antidepressants should be the only pharmacologic intervention used in the longer term.
	• The classes of antidepressants that have an evidence base for effectiveness are the SSRIs, SNRIs and TCAs.
	• Unless otherwise indicated, an SSRI (e.g., paroxetine, fluvoxamine, citalopram) licensed for panic disorder should be offered. If an SSRI is not suitable or there is no improvement after a 12-week course and if further medication is appropriate, imipramine or clomipramine may be considered.
	• If the patient is showing improvement, the medication should be continued for at least six months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.

American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[9]	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions,

Clinical Guideline	Recommendation(s)
	and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors. They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)[10]**	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • If screening suggests obsessive-compulsive symptoms, clinicians should fully evaluate the child using the DSM-IV-TR criteria and scalar assessment. • A complete psychiatric evaluation should be performed, including information from all available sources and compromising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • It is possible that three out of four children with obsessive-compulsive disorder (OCD) meet criteria for at least one comorbid diagnosis, and these children have lower response rates to CBT than children without comorbid diagnoses. • Identification of MDD and bipolar disorder is very important before initiating treatment with a SSRI. • Comorbid eating disorders are infrequent in younger children; however, comorbid eating disorders become more prevalent in adolescents. • A full medical, developmental, family and school history should be included with the psychiatric history and examination. • CBT is the first-line treatment for mild to moderate OCD in children, whenever

Clinical Guideline	Recommendation(s)
	possible. • For moderate to severe OCD, medication is indicated in addition to CBT. • Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children, including clomipramine (a TCA) and certain SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline). • There is no SRI that is proven to be more efficacious over another. • The modality of assigned treatment should be guided by empirical evidence on the moderators and predictors of treatment response. • Multimodal treatment with CBT and medication is recommended if CBT fails to achieve a clinical response after several months or in more severe cases. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. • Adding clomipramine to an SSRI is a useful medication augmentation strategy. • Augmenting with an atypical neuroleptic is also a strategy employed by experts (e.g. haloperidol and risperidone combined) based on studies in adults with OCD; however, controlled data for the use of atypical antipsychotics in children with OCD does not exist. • A minimum of two adequate SSRI trials or an SSRI and clomipramine trial is recommended before atypical augmentation. • Empirically validated medication and psychosocial treatments for comorbid disorders should be considered.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007; 2013 update)[11]**	<u>General considerations</u> • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. <u>Initial treatment options</u> • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, FDA warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. <u>Changing treatments and pursuing sequential treatment trials</u>

Clinical Guideline	Recommendation(s)
	• Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder (2010)**[12]	• The psychiatric evaluation of children and adolescents should routinely include questions about traumatic experiences and posttraumatic stress disorder (PTSD) symptoms. • If the evaluation indicates symptoms of PTSD, the clinician should formally determine if PTSD is present, the severity of PTSD symptoms and the degree of functional impairment. Caregivers should be included in the formal evaluation. • A differential diagnosis should be conducted in order to rule out diagnoses with symptoms that can mimic PTSD symptoms. • The treatment plan should be comprehensive in approach and should consider the severity of symptoms and impairment, as well as comorbid psychiatric conditions. • Trauma-focused psychotherapies should be considered first-line in children and adolescents with PTSD, including psychoanalytic, attachment and cognitive behavioral treatment models. • SSRIs can be considered for treatment of children and adolescents with PTSD. • The effect of SSRIs in children with PTSD may be more consistent with a placebo effect. • Other medications such as clonidine and propranolol may be useful in decreasing symptoms of hyperarousal, and anticonvulsants may beneficial in treating PTSD symptoms other than avoidance. • Benzodiazepines have not been found to be beneficial in treating PTSD symptoms. • School-based accommodations are recommended for children with PTSD, especially in children with school-based trauma, such as bullying. • The use of restrictive, “rebirthing,” binding or other coercive therapies are not recommended. • Screening for PTSD in the school or community should be conducted after traumatic events that affect significant numbers of children.
American Psychiatric Association: **Guideline Watch: Practice Guideline for the Treatment of Patients with Acute**	• Meta-analyses and several randomized controlled trials published since 2004 (2004 Guideline summarized below) support the greater efficacy of SSRIs and SNRIs over placebo for non-combat-related PTSD. • The evidence base for pharmacological intervention in combat-related PTSD has not been significantly augmented by recent studies. Studies suggest that SSRIs may not be recommended with the previous level of confidence for the

Clinical Guideline	Recommendation(s)
Stress Disorder and Posttraumatic Stress Disorder (2009)[13]	treatment of PTSD in this particular population. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment. • As described in the 2004 guideline, no significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available. Since that time, studies have been published comparing nefazodone and sertraline, venlafaxine and sertraline, the SNRI reboxetine and fluvoxamine, and fluoxetine, moclobemide, and tianeptine. These studies have generally demonstrated the greater efficacy of antidepressants to placebo but have done little to clarify the relative utility of these different antidepressants. • There is a relatively robust evidence basis for pharmacological treatment with antidepressant medications (particularly SSRIs and SNRIs for noncombat PTSD) as compared to other classes of medications. • Comparison of other treatments with the SSRIs and SNRIs is complicated by methodological differences in the available studies. SSRIs and SNRIs have mostly been studied in rigorous trials compared to placebo; other agents have been studied against "treatment as usual" or as augmentation agents in patients with refractory illness.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)[14]**	• Goals of treatment for patients with PTSD and acute stress disorder (ASD) include lessening the severity of symptoms and preventing trauma-related comorbid conditions. • Clinical trial data and randomized studies are limited and difficult to perform. • Treatment includes pharmacotherapy, psychotherapy and supportive measures. • SSRIs are first-line therapy for PTSD and ASD and if found effective, treatment should be continued in order to continue to see benefit. • Second-line treatment agents include TCAs (specifically amitriptyline and imipramine, but not desipramine) and MAOIs. • Benzodiazepines should not be used as monotherapy, but may be effective as sedatives and anxiolytics. • Atypical antipsychotics may be necessary for patients experiencing psychotic symptoms. • Anticonvulsants (divalproex, carbamazepine, topiramate and lamotrigine) have produced mixed results for treating PTSD and ASD but may prove to be beneficial. • Limited data exists for the use of adrenergic inhibitors and their use is not part of the guideline at this time. • An adequate trial of therapy requires a minimum of three months of treatment. If treatment is effective, it should be continued for up to 12 months or longer.
American Academy of Family Physicians: **Premenstrual Syndrome and Premenstrual Dysphoric Disorder (2016)[15]**	• SSRIs are first-line treatment for severe symptoms of PMS and PMDD. Sertraline, paroxetine, fluoxetine, citalopram, and escitalopram can be used to treat the psychiatric symptoms of PMS and PMDD and have been shown to relieve some of the physical symptoms. • Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) such as venlafaxine have been used off-label to treat PMDD in women with predominantly psychological symptoms. The effect is achieved over a relatively short period, three to four weeks, and sustained throughout subsequent menstrual cycles. • Studies have suggested that oral contraceptives provide benefit when treating physical and psychiatric symptoms of PMS or PMDD. Oral contraceptives with and without drospirenone seem to be effective at relieving abdominal bloating, mastalgia, headache, weight gain, and swelling of extremities. Trials that extend beyond three months are needed for further analysis. • Calcium supplementation has been evaluated as treatment for PMS. Women with PMS and mood instability have been noted to have associated cyclic changes in their calcium levels; the exact mechanism of action is unknown. • Although gonadotropin-releasing hormone agonists have been used since the

Clinical Guideline	Recommendation(s)
	1980s and are effective, they are not practical for long-term use because of the increased cardiovascular and osteoporosis risks associated with extended use. Long-term users often need hormone add-back therapy to counteract many of their hypoestrogenic effects, which may cause a return of PMS symptoms.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Eating Disorders (2023)**[16]	• Patients with anorexia nervosa who require nutritional rehabilitation and weight restoration should have individualized goals set for weekly weight gain and target weight. • Adults with anorexia nervosa should be treated with an eating disorder focused psychotherapy, which should include normalizing eating and weight control behaviors, restoring weight, and addressing psychological aspects of the disorder. • Adolescents and emerging adults with anorexia nervosa who have an involved caregiver should be treated with eating disorder-focused family-based treatment, which should include caregiver education aimed at normalizing eating and weight control behaviors and restoring weight. • Adults with bulimia nervosa should be treated with eating disorder-focused cognitive-behavioral therapy and a serotonin reuptake inhibitor (e.g., 60 mg fluoxetine daily) should also be prescribed, either initially or if there is minimal or no response to psychotherapy alone by six weeks of treatment. o Other SSRI antidepressants may be used in patients who are unable to tolerate fluoxetine or who prefer a different medication; however, evidence is limited on the effects of other SSRIs or other antidepressants in bulimia nervosa. • Adolescents and emerging adults with bulimia nervosa who have an in-\volved caregiver should be treated with eating disorder-focused family-based treatment. • Patients with binge-eating disorder should be treated with eating disorder-focused cognitive-behavioral therapy or interpersonal therapy, in either individual or group formats. • Adults with binge-eating disorder who prefer medication or have not responded to psychotherapy alone should be treated with either an antidepressant medication or lis-dexamfetamine.
American College of Physicians: **Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain (2017)**[17]	• Given that most patients with acute or subacute low back pain improve over time regardless of treatment, select nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation. If pharmacologic treatment is desired, select nonsteroidal anti-inflammatory drugs (NSAIDs) or skeletal muscle relaxants. • For patients with chronic low back pain, initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation. Nonpharmacologic interventions are considered as first-line options in patients with chronic low back pain because fewer harms are associated with these types of therapies than with pharmacologic options. • Pharmacologic therapy should be considered for patients with chronic low back pain who do not improve with nonpharmacologic interventions. In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, consider pharmacologic treatment with NSAIDs as first-line therapy, or tramadol or duloxetine as second-line therapy. Only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients.

Clinical Guideline	Recommendation(s)
American College of Rheumatology/Arthritis Foundation: **Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee (2019)[18]**	Pharmacological Management • Topical NSAIDs are strongly recommended for patients with knee osteoarthritis and conditionally recommended for patients with hand osteoarthritis. • Topical capsaicin is conditionally recommended for patients with knee osteoarthritis and conditionally recommended against in patients with hand osteoarthritis. • Oral NSAIDs are strongly recommended for patients with knee, hip, and/or hand osteoarthritis. • Intraarticular glucocorticoid injections are strongly recommended for patients with knee and/or hip osteoarthritis and conditionally recommended for patients with hand osteoarthritis. • Ultrasound guidance for intraarticular glucocorticoid injection is strongly recommended for injection into hip joints. • Intraarticular glucocorticoid injections versus other injections are conditionally recommended for patients with knee, hip, and/or hand osteoarthritis. • Acetaminophen is conditionally recommended for patients with knee, hip, and/or hand osteoarthritis. • Duloxetine is conditionally recommended for patients with knee, hip, and/or hand osteoarthritis. • Tramadol is conditionally recommended for patients with knee, hip, and/or osteoarthritis. • Non-tramadol opioids are conditionally recommended against in patients with knee, hand, and/or hip osteoarthritis with the recognition that they may be used under certain circum-stances, particularly when alternatives have been exhausted. • Colchicine is conditionally recommended against in patients with knee, hip, and/or hand osteoarthritis. • Fish oil is conditionally recommended against in patients with knee, hip, and/or hand osteoarthritis. • Vitamin D is conditionally recommended against in patients with knee, hip, and/or hand osteoarthritis. • Bisphosphonates are strongly recommended against in patients with knee, hip, and/or hand osteoarthritis. • Glucosamine is strongly recommended against in patients with knee, hip, and/or hand osteoarthritis. • Chondroitin sulfate is strongly recommended against in patients with knee and/or hip osteoarthritis as are combination products that include glucosamine and chondroitin sulfate, but is conditionally recommended for patients with hand osteoarthritis. • Hydroxychloroquine is strongly recommended against in patients with knee, hip, and/or hand osteoarthritis • Methotrexate is strongly recommended against in patients with knee, hip, and/or hand osteoarthritis. • Intraarticular hyaluronic acid injections are conditionally recommended against in patients with knee and/or first carpometacarpal joint osteoarthritis and strongly recommended against in patients with hip osteoarthritis. • Intraarticular botulinum toxin injections are conditionally recommended against in patients with knee and/or hip osteoarthritis. • Prolotherapy is conditionally recommended against in patients with knee and/or hip osteoarthritis. • Platelet-rich plasma treatment is strongly recommended against in patients with knee and/or hip osteoarthritis. • Stem cell injections are strongly recommended against in patients with knee and/or hip osteoarthritis • Tumor necrosis factor inhibitors and interleukin-1 receptor antagonists are

Clinical Guideline	Recommendation(s)
	strongly recommended against in patients with knee, hip, and/or hand osteoarthritis.

European League Against Rheumatism: **Evidence-based Recommendations for the Management of Fibromyalgia (2016)**[19]	• Optimal management requires prompt diagnosis. Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context. It should be recognized as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features. In general, the management of fibromyalgia should take the form of a graduated approach.
	• Management of fibromyalgia should aim at improving health-related quality of life balancing benefit and risk of treatment that often requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features (such as depression), fatigue, sleep disturbance, and patient preferences and comorbidities; by shared decision-making with the patient. Initial management should focus on non-pharmacological therapies.
	• Non-pharmacological management
	  ○ Aerobic and strengthening exercise (only recommendation designated as 'strong for'; all others are 'weak for')
	  ○ Cognitive behavioral therapies
	  ○ Multicomponent therapies
	  ○ Defined physical therapies: acupuncture or hydrotherapy
	  ○ Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction
	• Pharmacological management
	  ○ Amitriptyline (low dose)
	  ○ Duloxetine or milnacipran
	  ○ Tramadol
	  ○ Pregabalin
	  ○ Cyclobenzaprine
	• Several pharmacological therapies including NSAIDs, MAOIs and SSRIs were not recommended because of lack of efficacy, and a 'strong against' evaluation was specifically given to growth hormone, sodium oxybate, strong opioids and corticosteroids based on lack of efficacy and high risk of side effects.

American Academy of Neurology **Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary (2022)**[20]	• Clinicians should assess patients with diabetes for peripheral neuropathic pain and its effect on these patients' function and quality of life. • When initiating pharmacologic intervention for painful diabetic polyneuropathy, clinicians should counsel patients that the goal of therapy is to reduce, and not necessarily to eliminate, pain. • Clinicians should assess patients with painful diabetic polyneuropathy for the presence of concurrent mood and sleep disorders and treat them as appropriate. • In patients with painful diabetic polyneuropathy, clinicians should offer TCAs, SNRIs, gabapentinoids, and/or sodium channel blockers to reduce pain. • Clinicians may assess patient preferences for effective oral, topical, nontraditional, and nonpharmacologic interventions for painful diabetic polyneuropathy. • In patients preferring topical, nontraditional, or nonpharmacologic interventions, providers may offer topical, nontraditional, or nonpharmacologic interventions. • Given similar efficacy, clinicians should consider factors other than efficacy, including potential adverse effects, patient comorbidities, cost, and patient preferences, when recommending treatment for painful diabetic polyneuropathy. • In patients of childbearing potential with painful diabetic polyneuropathy, clinicians should not offer valproic acid.

Clinical Guideline	Recommendation(s)
	• In all patients with painful diabetic polyneuropathy, clinicians should not prescribe valproic acid given the potential for serious adverse events unless multiple other effective medications have failed. • Clinicians should counsel patients that a series of medications may need to be tried to identify the treatment that most benefits patients with painful diabetic polyneuropathy. • Clinicians should determine that an individual intervention to reduce neuropathic pain is a failure either when the medication has been titrated to a demonstrated efficacious dose for approximately 12 weeks without clinically significant pain reduction or when side effects from the medication outweigh any benefit in reduced neuropathic pain. • Clinicians should offer patients a trial of a medication from a different effective class when they do not achieve meaningful improvement or if they experience significant adverse effects with the initial therapeutic class. • For patients who achieve partial improvement with an initial therapeutic class, clinicians should offer a trial of a medication from a different effective class or combination therapy by adding a medication from a different effective class. • Clinicians should not use opioids for the treatment of painful diabetic polyneuropathy. • If patients are currently on opioids for the treatment of painful diabetic polyneuropathy, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies. • Clinicians should not use tramadol and tapentadol (opioids/ SNRI dual mechanism agents) for the treatment of painful diabetic polyneuropathy. • If patients are currently on tramadol and tapentadol (opioids/ SNRI dual mechanism agents) for the treatment of painful diabetic polyneuropathy, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[21]	Painful polyneuropathy • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. • Recommended first-line treatments include tricyclic antidepressants (TCA), gabapentin, pregabalin, and SNRIs (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. • Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. • In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. Post herpetic neuropathy • Recommended first-line treatments include a TCA, gabapentin, or pregabalin. • Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. • Strong opioids and capsaicin cream are recommended as second-line therapies.
American Diabetes Association: **Retinopathy, Neuropathy, and Foot Care: Standards of Medical Care in**	Neuropathy Treatment • Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes and to slow the progression of neuropathy in patients with type 2 diabetes. • Assess and treat patients to reduce pain related to diabetic peripheral neuropathy and symptoms of autonomic neuropathy and to improve quality of life.

Clinical Guideline	Recommendation(s)
Diabetes - 2022 (2022)[22]	• Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. • Given the high risk for addiction and safety concerns compared with the relatively modest pain reduction, the use of extended-release tapentadol is not generally recommended as a first-or second line therapy. • The use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided. • Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin, although not approved for the treatment of painful diabetic polyneuropathy, may be effective and considered for the treatment of painful diabetic polyneuropathy.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antidepressants 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 Antidepressants[1-3]

Generic Name(s)	Depression /Major Depressive Disorder	Generalized Anxiety Disorder	Mixed Anxiety/ Depressive Disorder	Obsessive-Compulsive Disorder	Panic Disorder	Postpartum Depression	Posttraumatic Stress Disorder	Premenstrual Dysphoric Disorder	Seasonal Affective Disorder	Social Anxiety Disorder	Other
Monoamine Oxidase Inhibitors											
Isocarboxazid	✔										
Phenelzine	✔										
Selegiline	✔										
Tranylcypromine	✔										
Selective Serotonin- and Norepinephrine-reuptake Inhibitors											
Desvenlafaxine	✔										
Duloxetine	✔	✔									Chronic musculoskeletal pain; fibromyalgia*; neuropathic pain associated with diabetic peripheral neuropathy
Levomilnacipran	✔										
Venlafaxine	✔	✔ ‡			✔ ‡					✔ ‡	
Selective Serotonin-reuptake Inhibitors											
Citalopram	✔										
Escitalopram	✔	✔									
Fluoxetine	✔			✔	✔						Bulimia nervosa
Fluvoxamine				✔							
Paroxetine	✔	✔ §		✔ §	✔		✔ §	✔ ‡		✔	Moderate to severe vasomotor symptoms associated with menopause ‖
Sertraline	✔			✔	✔		✔	✔		✔	
Serotonin Modulators											
Nefazodone	✔										
Trazodone	✔										
Vilazodone	✔										
Vortioxetine	✔										
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents											
Amitriptyline	✔										
Amoxapine	✔										
Clomipramine				✔							
Desipramine	✔										
Doxepin	✔		✔								Insomnia¶
Imipramine	✔										Pediatric nocturnal enuresis
Nortriptyline	✔										

Generic Name(s)	Depression /Major Depressive Disorder	Generalized Anxiety Disorder	Mixed Anxiety/ Depressive Disorder	Obsessive-Compulsive Disorder	Panic Disorder	Postpartum Depression	Posttraumatic Stress Disorder	Premenstrual Dysphoric Disorder	Seasonal Affective Disorder	Social Anxiety Disorder	Other
Protriptyline	✔										
Trimipramine	✔										
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products											
Amitriptyline and chlordiazepoxide			✔								
Antidepressants, Miscellaneous											
Brexanolone						✔					
Bupropion	✔								✔ ‡		Smoking cessation‡
Dextromethorphan and bupropion	✔										
Esketamine	✔ #										
Mirtazapine	✔										

*Excluding Irenka® formulation.
‡Extended-release formulation only.
§Immediate-release formulation only.
‖7.5 mg capsule formulation only.
¶ Silenor® formulation only.
# Treatment-resistant depression or depressive symptoms with major depressive disorder with acute suicidal ideation or behavior

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Antidepressants[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Monoamine Oxidase Inhibitors					
Isocarboxazid	Not reported	Not reported	Liver	Renal	Not reported
Phenelzine	Not reported	Not reported	Liver	Renal (79)	11.6
Selegiline	25 to 30	90	Liver	Renal (10) Feces (2)	18 to 25
Tranylcypromine	Not reported	Not reported	Not reported	Renal	1.5 to 3.5
Selective Serotonin- and Norepinephrine-reuptake Inhibitors					
Desvenlafaxine	80	30	Liver	Renal (45)	10 to 11
Duloxetine	30 to 80	>90	Liver	Renal (70) Feces (20)	8 to 17
Levomilnacipran	92	22	Liver	Renal (85)	12
Venlafaxine	12.6 to 45.0	27 to 30	Liver	Renal (87) Feces (2)	5
Selective Serotonin-reuptake Inhibitors					
Citalopram	80	80	Liver	Renal (20) Feces	24 to 48
Escitalopram	80	56	Liver	Renal (8)	22 to 32
Fluoxetine	100	95	Liver	Renal (60) Feces (12)	96 to 144
Fluvoxamine	53	80	Liver	Renal (94)	15 to 16
Paroxetine	Completely absorbed	93 to 95	Liver	Renal (64 to 67) Feces (36 to 37)	15 to 22
Sertraline	Not reported	99	Liver	Renal (40 to 45) Feces (40 to 45)	24
Serotonin Modulators					
Nefazodone	20	>99	Liver	Renal (55) Feces (20 to 30)	1.9 to 5.3
Trazodone	65	89 to 95	Liver	Renal (70 to 75) Feces (21)	7 to 8
Vilazodone	72	96 to 99	Liver	Renal (1) Feces (2)	25
Vortioxetine	75	98	Liver	Renal (59) Feces (26)	66
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents					
Amitriptyline	100	90 to 95	Liver	Renal (18)	9 to 25
Amoxapine	18 to 54	90	Liver	Renal (69) Feces (18)	8
Clomipramine	20 to 78	97	Liver	Renal (51 to 60) Feces (24 to 32)	19 to 37
Desipramine	Not reported	Not reported	Liver	Renal (70)	14.3 to 24.7
Doxepin	Not reported	79 to 84	Liver	Bile	16.8
Imipramine	94 to 96	89	Liver	Renal	6 to 18
Nortriptyline	60	86 to 95	Liver	Renal (2) Bile	15 to 39
Protriptyline	Not reported	Not reported	Liver	Renal (50)	54 to 198
Trimipramine	Not reported	95	Liver	Renal	23
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products					

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amitriptyline and chlordiazepoxide	100	90 to 98	Liver	Renal (18)	9.0 to 27.0; 6.6 to 48.0
Antidepressants, Miscellaneous					
Brexanolone	<5	>99	Liver	Renal (42) Feces (47)	9
Bupropion	Not reported	84	Liver	Renal (87)	14 to 21
Dextromethorphan and bupropion	Not reported	D: 60 to 70 B: 84	Liver	D: Renal (37 to 83) B: Renal (87)	D: 22 B: 15
Esketamine	48	43 to 45	Liver	Renal (≥78) Feces (≤2)	7 to 12
Mirtazapine	50	85	Liver	Renal (75) Feces (15)	20 to 40

V. Drug Interactions

Major drug interactions with the antidepressants are listed in Table 5.

Table 5. Major Drug Interactions with the Antidepressants[2]

Generic Name(s)	Interaction	Mechanism
MAOIs		
MAOIs	Central nervous system depressants (e.g., alcohol, barbiturates, narcotics)	Severe hypertension may occur. Concurrent use is contraindicated.
MAOIs	Central nervous system stimulants (e.g., amphetamines, cocaine, methylphenidate, dexmethylphenidate)	Hypertensive crisis may occur. Coadministration is contraindicated.
MAOIs	MAOIs	Do not administer MAOIs with other MAOIs because hypertensive crisis and convulsive seizures, coma, or circulatory collapse may occur.
MAOIs	Methylphenidates	Pharmacological effects of methylphenidates may be increased by MAOIs. Headache, gastrointestinal symptoms and hypertension may occur. Concomitant use of methylphenidates and MAOIs is contraindicated.
MAOIs	Norepinephrine reuptake inhibitors (including tapentadol)	Coadministration may increase risk of toxic effects. Serious and sometimes fatal reactions have occurred. Use of norepinephrine reuptake inhibitors within 14 days of MAOIs is contraindicated.
MAOIs	SNRIs and SSRIs	A serotonin syndrome may occur. Concomitant use is contraindicated. At least 14 days should elapse between discontinuation of a MAOI and the start of an SSRI or vice versa. Allow at least five weeks between discontinuation of fluoxetine and initiation of a MAOI and at least 14 days between discontinuation of a MAOI and initiation of fluoxetine.
MAOIs	Sympathomimetics	The MAOIs' potentiation of indirect- or mixed-acting sympathomimetic substances, including anorexiants, may result in severe headache,

Generic Name(s)	Interaction	Mechanism
		hypertension, high fever, and hyperpyrexia, possibly resulting in hypertensive crisis; avoid coadministration.
MAOIs	TCAs	Do not administer MAOIs with or immediately following TCAs. There have been reports of serious, sometimes fata, reactions. These reactions include hyperthermia, rigidity, myoclonus, autonomic instability with possible vital sign fluctuations, and mental status changes that can include extreme agitation and confusion progressing to delirium and coma.
MAOIs	Triptans	Prolonged vasospastic reaction is a possibility when triptans and MAOIs are coadministered. The potential for development of serotonin syndrome also exists. Coadministration is not recommended.
MAOIs	Apraclonidine	Coadministration of MAOIs and apraclonidine is contraindicated. MAOIs and apraclonidine should not be administered within 14 days of discontinuation of either agent.
MAOIs	Atomoxetine	Toxic effects may be increased with concurrent administration of atomoxetine and MAOIs. Serious and sometimes fatal reactions have occurred. Use of atomoxetine within 14 days of MAOIs is contraindicated.
MAOIs	Bupropion	Coadministration is contraindicated. Risk of acute bupropion toxicity may be increased. Allow at least 14 days to elapse between discontinuing an MAOI and starting bupropion.
MAOIs	Buspirone	The risk of hypertension induced by MAOIs may be increased by co-administration of buspirone. It should be noted for selegiline that only higher dosages participate in this interaction. Allow at least 10 days between discontinuation of isocarboxazid and institution of buspirone.
MAOIs	Cyclobenzaprine	Because cyclobenzaprine is structurally related to the TCAs, use with caution with MAOIs. It should be noted for selegiline that only higher doses participate in this interaction.
MAOIs	Dextromethorphan	Hyperpyrexia, abnormal muscle movement, psychosis, bizarre behavior, hypotension, coma, and death have been associated with this combination.
MAOIs	Levodopa	Hypertensive reactions occur if levodopa is given to patients receiving MAOIs.
MAOIs	Linezolid	Adverse effects may be increased with concurrent administration of linezolid and MAOIs.
MAOIs	Meperidine	Coadministration of these agents may result in agitation, seizures, diaphoresis, and fever with the potential to progress to coma, apnea, and death. Reactions may be delayed and occur several weeks following withdrawal of MAOIs. Avoid this combination. Administer other narcotic analgesics with caution.
MAOIs	Nefazodone	The combination of MAOIs and nefazodone is contraindicated. The combination may be useful

Generic Name(s)	Interaction	Mechanism
		for treating depression; however, unexpected toxicity may occur.
MAOIs	Tetrabenazine	The combination of MAOIs and tetrabenazine may produce severe unexpected toxicity. Coadministration is contraindicated.
MAOIs	Tramadol	Coadministration may enhance seizure risk, and/or cause a severe reaction potentially involving the respiratory, cardiac, and central nervous system. Avoid coadministration.
MAOIs	Trazodone	The potential for the development of serotonin syndrome exists with concurrent use of MAOIs and trazodone.
MAOIs	Vilazodone	Do not administer MAOIs and vilazodone within 14 days of one another. Serotonin syndrome may result from concurrent administration.
MAOIs	Vortioxetine	Coadministration of MAOI used to treat psychiatric disorders and vortioxetine is contraindicated in the official package labeling of vortioxetine. In addition, the initiation of vortioxetine in patients receiving linezolid is contraindicated. Serotonin syndrome (unexpected irritability, increased muscle tone, altered consciousness and myoclonus) may result from concurrent administration.
MAOIs (selegiline)	Methadone	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering methadone to patients receiving selegiline. At least 14 days should elapse between discontinuation of selegiline and administration of methadone.
MAOIs	Insulins	The hypoglycemic effect of insulin may be increased by MAOIs.
MAOIs	Meglitinides	The hypoglycemic effects of meglitinides may be increased by MAOIs.
MAOIs	Sulfonylureas	MAOIs enhance the hypoglycemic action of sulfonylureas.
MAOIs	Carbamazepine	While the manufacturer's data states that carbamazepine is contraindicated with MAOIs, other conflicting data suggest safe coadministration. It should be noted that only higher doses of selegiline (e.g. antidepressant doses) participate in this interaction.
MAOIs	Ginseng	Use of MAOIs with ginseng may produce unexpected toxic effects.
MAOIs	Tryptophan	Coadministration may result in hyperreflexia, confusion, disorientation, shivering, myoclonic jerks, agitation, amnesia, delirium, hypomanic signs, ataxia, ocular oscillations, Babinski signs.
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	COMT inhibitors	The combination of these MAOIs with COMT inhibitors may result in inhibition of the majority of pathways responsible for normal catecholamine metabolism. Excessive sympathetic stimulation may result. Coadministration of COMT inhibitors and non-selective MAOIs is not recommended.

Generic Name(s)	Interaction	Mechanism
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	Narcotic analgesics	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering narcotic analgesics to patients receiving these MAOIs. At least 14 days should elapse after discontinuation of an MAOI before initiation of treatment with a narcotic analgesic.
SNRIs		
SNRIs	MAOIs	Coadministration of SNRIs and MAOIs is contraindicated. Serious, sometimes fatal, reactions may occur, including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. It is recommended that SNRIs not be used within at least 14 days of discontinuing treatment with an MAOI.
SNRIs	Linezolid	Serotonin syndrome may occur, possibly due to excessive accumulation of serotonin. Initiation of an SNRI is contraindicated in patients receiving linezolid.
SNRIs	Methylene blue	Coadministration of methylene blue and desvenlafaxine may increase the risk of central nervous system toxicity, including serotonin syndrome.
SNRIs	Tramadol	Increased risk of seizures is a possibility when tramadol and SNRIs are coadministered. Serotonin syndrome is also a risk with this combination. Concomitant use is not recommended.
SNRIs (duloxetine)	Phenothiazines (thioridazine)	Plasma concentrations and pharmacologic effects of thioridazine may be increased by duloxetine. The possibility of serious ventricular dysrhythmias should be considered. Do not coadminister.
SNRIs (duloxetine)	Tamoxifen	Pharmacologic effects of Tamoxifen may be decreased by Duloxetine. Coadministration of Duloxetine with Tamoxifen may increase the risk of breast cancer recurrence.
SNRIs	Anticoagulants	The risk of bleeding with Anticoagulants may be potentiated with concomitant use of these SNRIs and patients are at an increased risk of bleeding. The mechanism of this interaction is unknown.
SNRIs	SSRIs	The development of serotonin syndrome is possible when the combination of SNRIs and serotonin reuptake blockers are coadministered. In addition, plasma concentrations of SNRIs may be increased by serotonin reuptake blockers.
SNRIs	Iobenguane	SNRIs may reduce uptake and diagnostic efficacy of Iobenguane. False-negative Iobenguane imaging tests may result.
SNRIs	L-Tryptophan	Coadministration may lead to the development of serotonin syndrome.
SNRIs (desvenlafaxine,	NSAIDs	The toxic effects may be increased with concurrent administration of NSAIDs and

Generic Name(s)	Interaction	Mechanism
venlafaxine)		desvenlafaxine/venlafaxine. The risk of upper gastrointestinal bleeding may be increased. Patients taking concurrent SNRIs and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.
SNRIs (desvenlafaxine, venlafaxine)	Salicylates	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of salicylates and desvenlafaxine or venlafaxine. The mechanism is unknown. Prolonged use of desvenlafaxine or venlafaxine may lead to depletion of serotonin, which is thought to play an important role in hemostasis.
SNRIs (desvenlafaxine, venlafaxine)	Cyproheptadine	Decreased pharmacologic effects of venlafaxine may result. Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level.
SNRIs (desvenlafaxine, venlafaxine)	Lithium	Coadministration of lithium and desvenlafaxine or venlafaxine may cause central nervous system toxicity, including serotonin syndrome. Serum lithium concentrations may be increased due to increased serotonergic neurotransmission.
SNRIs (desvenlafaxine, venlafaxine)	St. John’s wort	Unexpected toxicity may occur when St. John's wort and desvenlafaxine/ venlafaxine are coadministered; the mechanism is unknown.
SNRIs (desvenlafaxine, venlafaxine)	Trazodone	Unexpected toxic effects may occur when trazodone is combined with desvenlafaxine or venlafaxine. The mechanism is unknown.
SNRIs (duloxetine)	TCAs	Plasma concentrations of TCAs may be increased by duloxetine. Inhibition of cytochrome CYP2D6 isoenzymes by duloxetine may decrease the metabolic elimination of TCAs.
SNRIs (duloxetine)	Ciprofloxacin	Plasma concentrations and pharmacologic effects of duloxetine may be increased when coadministered with ciprofloxacin. Inhibition of CYP1A2 by ciprofloxacin may decrease the metabolic elimination of duloxetine.
SNRIs (duloxetine)	Flecainide	Plasma concentrations of flecainide may be increased by duloxetine. Clinical outcome is unknown.
SNRIs (duloxetine)	Propafenone	Plasma concentrations of propafenone may be increased by duloxetine due to inhibition of CYP2D6 isoenzymes.
SNRIs (levomilnacipran)	Alcoholic beverages	Consumption of alcohol may interfere with the delayed release mechanism of levomilnacipran.
SNRIs (venlafaxine)	Bupropion	Unexpected adverse effects, including serotonin syndrome, may occur when Venlafaxine and Bupropion are coadministered. The mechanism of this interaction is unknown.
SNRIs (venlafaxine)	Terbinafine	Plasma concentrations and pharmacologic effects of venlafaxine may be increased when coadministered with terbinafine. The potential for adverse effects due to venlafaxine may be increased. Inhibition of CYP2D6-mediated metabolism of venlafaxine by terbinafine is suspected.
SSRIs		

Generic Name(s)	Interaction	Mechanism
SSRIs	Linezolid	Serotonin syndrome may occur as a result of excessive accumulation of serotonin. The coadministration of linezolid and SSRIs should be handled with caution.
SSRIs	Tramadol	Increased risk of seizures is possible when tramadol and SSRIs are coadministered. Serotonin syndrome is also a potential risk when tramadol and SSRIs are coadministered.
SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	Clozapine	These SSRIs may increase plasma concentrations and pharmacologic effects of clozapine. Severe toxicity may occur. Inhibition of cytochrome P450 1A2 isoenzymes by these SSRIs may decrease the metabolic elimination of clozapine.
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline)	Pimozide	Plasma concentrations of pimozide may be increased by SSRIs. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
SSRIs (fluoxetine, fluvoxamine paroxetine)	Phenothiazines (chlorpromazine, thioridazine)	Pharmacologic effects and plasma concentrations of phenothiazines may be increased by SSRIs. Neurologic toxicity, including extrapyramidal effects, and cardiac toxicity, including the potential for torsade de pointes, may occur.
SSRIs (fluoxetine, paroxetine sertraline)	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by certain SSRIs. Coadministration may increase the risk of breast cancer recurrence.
SSRIs (citalopram, escitalopram)	Cimetidine	Pharmacologic effects and plasma concentrations of citalopram may be increased by cimetidine. Cimetidine may inhibit the metabolic and/or renal elimination of citalopram.
SSRIs (citalopram, fluoxetine)	Nilotinib	Additive QT prolongation may occur during coadministration of vandetanib and certain SSRIs. The black box warning contained in the official package labeling for vandetanib states that the use of vandetanib with medications that prolong the QT interval should be avoided.
SSRIs (citalopram, fluoxetine)	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and certain SSRIs. The black box warning contained in the official package labeling for vandetanib states that the use of vandetanib with medications that prolong the QT interval should be avoided.
SSRIs (fluvoxamine)	Ramelteon	Plasma concentrations of ramelteon may be increased by coadministration of fluvoxamine. Coadministration of fluvoxamine and ramelteon is contraindicated.
SSRIs (fluvoxamine)	Tizanidine	Tizanidine plasma concentrations and pharmacologic effects may be increased by fluvoxamine. Adverse effects associated with tizanidine, including significant hypotension, may be expected. Concomitant use is contraindicated.
SSRIs	Anticoagulants	The risk of bleeding with anticoagulants may be potentiated with concomitant use of SSRIs and patients are at an increased risk of bleeding.
SSRIs	NSAIDs	Toxic effects may be increased with concurrent

Generic Name(s)	Interaction	Mechanism
		administration of NSAIDs and SSRIs. The risk of upper gastrointestinal bleeding may be increased. Patients taking both SSRIs and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.
SSRIs	Salicylates	Toxic effects may be increased with concurrent administration of salicylates and SSRIs. The risk of upper gastrointestinal bleeding may be increased. Patients taking both salicylates and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.
SSRIs	SNRIs	Serotonin syndrome has been reported during coadministration of SSRIs and SNRIs. If coadministration is necessary, the patient should be closely monitored, especially when starting treatment of increasing doses. Plasma concentrations of duloxetine may be increased by CYP2D6 inhibitors, such as fluoxetine and paroxetine.
SSRIs	Cyproheptadine	Decreased pharmacologic effects of SSRIs may result. Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level.
SSRIs	L-tryptophan	Coadministration may lead to the development of serotonin syndrome.
SSRIs	St. John’s wort	Unexpected toxicity may occur when St. John's wort and SSRIs are coadministered.
SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	Beta-blockers	Coadministration of SSRIs and beta-blockers may increase risk of bradycardia and hypotension.
SSRIs (fluoxetine, sertraline)	Bupropion	Unexpected adverse effects, including serotonin syndrome, may occur when these SSRIs and bupropion are coadministered. The mechanism of this interaction is unknown.
SSRIs (fluoxetine, sertraline)	Carbamazepine	Plasma concentrations and pharmacologic effects of carbamazepine may be increased by these SSRIs. Toxicity may occur. Toxic serotonin syndrome may also occur.
SSRIs (fluoxetine, paroxetine)	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by these SSRIs. A modification of the iloperidone dose is recommended.
SSRIs (fluoxetine, paroxetine)	Risperidone	These SSRIs may increase plasma concentrations and pharmacologic effects of risperidone. Additionally, concomitant use has resulted in reported cases of serotonin syndrome. Worsening of obsessive-compulsive disorder has also been reported with combined use.
SSRIs (fluoxetine, paroxetine)	Tetrabenazine	Plasma concentrations and pharmacologic effects of tetrabenazine may be increased by these SSRIs. Dosage adjustment is recommended.
SSRIs (fluoxetine)	HIV protease inhibitors	HIV protease inhibitors may increase plasma concentrations of fluoxetine resulting in possible fluoxetine toxicity. Similarly, fluoxetine may

Generic Name(s)	Interaction	Mechanism
		increase plasma concentrations of HIV protease inhibitors.
SSRIs (fluoxetine)	Hydantoins	Serum hydantoin concentrations may be elevated. Close monitoring of hydantoin levels and observing patients for toxicity or loss of therapeutic activity if fluoxetine is started or stopped is advised. Fosphenytoin may enhance QTc-prolonging effect of fluoxetine.
SSRIs (fluvoxamine)	Theophyllines	Pharmacological effects of the theophyllines may be increased by fluvoxamine. Elevated theophylline concentrations and toxicity including nausea, vomiting, cardiovascular instability and seizures may occur.
SSRIs (paroxetine)	Abiraterone	Plasma concentrations and pharmacologic effects of paroxetine may be increased by abiraterone, due to the inhibition of CYP2D6 by abiraterone.
Serotonin Modulators		
Serotonin modulators	MAOIs	Coadministration of the Serotonin Modulators and MAOIs is contraindicated due to increased risk for serotonin syndrome.
Serotonin modulators	Linezolid	Coadministration of the Serotonin Modulators and linezolid is contraindicated due to risk of serotonin syndrome.
Serotonin modulators (vilazodone, vortioxetine)	Methylene blue	Coadministration of certain Serotonin Modulators may increase the risk of central nervous system toxicity, including serotonin syndrome. Initiation of certain Serotonin Modulators in patients receiving methylene blue is contraindicated.
Nefazodone	Statins	The risk of rhabdomyolysis and myositis may be increased with certain statins. Coadministration of nefazodone with lovastatin or simvastatin is contraindicated.
Nefazodone	Tyrosine kinase receptor inhibitors	Plasma concentrations and pharmacologic effects of tyrosine kinase receptor inhibitors may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Vasopressin receptor agonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by nefazodone. Coadministration of nefazodone and conivaptan or tolvaptan is contraindicated.
Nefazodone	Colchicine	Plasma concentrations of colchicine may be increased by nefazodone and life-threatening and fatal colchicine toxicity may occur. Dosage adjustment of colchicine is required for coadministration of these agents. Coadministration is contraindicated in patients with renal or hepatic impairment.
Nefazodone	Docetaxel	Plasma concentrations and pharmacologic effects of docetaxel may be increased by nefazodone. Use of nefazodone with docetaxel may increase the risk and/or severity of docetaxel-related toxicity. Coadministration should be avoided.
Nefazodone	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by nefazodone. Coadministration is contraindicated.

Generic Name(s)	Interaction	Mechanism
Nefazodone	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be increased by nefazodone. Coadministration is contraindicated.
Nefazodone	Pimozide	Pharmacologic effects of pimozide may be increased by nefazodone. Elevated plasma concentrations and cardiovascular toxicity may occur. Coadministration is contraindicated.
Nefazodone	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased when coadministered with nefazodone. Coadministration is contraindicated.
Nefazodone	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be increased by nefazodone. Coadministration of nefazodone and ticagrelor should be avoided according to official package labeling.
Nefazodone	Toremifene	Plasma concentrations and pharmacologic effects of toremifene may be increased by nefazodone. Toxicity, including QT prolongation may occur. Coadministration of nefazodone and toremifene should be avoided according to a black box warning in official package labeling.
Trazodone	Sodium oxybate	Concurrent use of sodium oxybate and trazodone may result in an increase in sleep duration and central nervous system depression. Coadministration is contraindicated.
Vilazodone	Tramadol	Increased risk of seizures is listed in the manufacturer's package labeling as a possibility when tramadol and vilazodone are coadministered. Serotonin syndrome is also a potential risk with this combination.
Serotonin modulators (nefazodone, vilazodone, vortioxetine)	Triptans	Coadministration of certain serotonin modulators and Triptans may cause central nervous system toxicity, and rarely, serotonin syndrome.
Serotonin modulators (nefazodone, vilazodone)	Narcotic analgesics	Plasma concentrations and pharmacologic effects of some narcotic analgesics may be increased by certain serotonin modulators. Toxic effects of vilazodone may be increased by fentanyl, resulting in the development of serotonin syndrome.
Serotonin modulators (trazodone, vilazodone)	HIV protease inhibitors	HIV protease inhibitors may increase the plasma concentration of trazodone and vilazodone.
Nefazodone	Benzodiazepines	Nefazodone may increase the pharmacologic effects of certain benzodiazepines. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations.
Nefazodone	MTOR inhibitors	Pharmacologic effects of MTOR inhibitors may be increased by nefazodone. Official package labeling for MTOR inhibitors states that coadministration with strong CYP3A4 inhibitors, such as nefazodone, should be avoided.
Nefazodone	Muscarinic receptor antagonists	Plasma concentrations and pharmacologic effects of muscarinic receptor antagonists may be

Generic Name(s)	Interaction	Mechanism
		increased by nefazodone. Official package labeling recommends a reduced maximum dose of muscarinic receptor antagonists in patients receiving strong CYP3A4 inhibitors, such as nefazodone.
Nefazodone	Brentuximab	Plasma concentrations and pharmacologic effects of brentuximab may be increased by nefazodone. The inhibition of CYP3A4 by nefazodone may increase the plasma concentrations of monomethyl auristatin E, the microtubule disrupting agent in brentuximab.
Nefazodone	Budesonide	Plasma concentrations and pharmacologic effects of oral or inhaled budesonide may be increased by nefazodone. Corticosteroid toxicity and/or adrenal suppression may occur.
Nefazodone	Buspirone	Plasma concentrations and pharmacologic effects of buspirone may be increased by nefazodone. The risk of buspirone-induced adverse reactions may be increased. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of buspirone.
Nefazodone	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Cilostazol	Plasma concentration and pharmacologic effects of cilostazol may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Cyclosporine	Cyclosporine concentration and pharmacologic effects may be increased by nefazodone. Cyclosporine toxicity may occur.
Nefazodone	Eszopiclone	Plasma concentrations and the pharmacologic effects of eszopiclone may be increased by nefazodone.
Nefazodone	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by nefazodone. A modification of the iloperidone dose is recommended.
Nefazodone	Ivacaftor	Plasma concentrations and pharmacologic effects of ivacaftor may be increased by nefazodone. A reduction in the ivacaftor dose is recommended in patients receiving both medications according to the official package labeling.
Nefazodone	Ixabepilone	The pharmacologic effects of epothilones may be increased by nefazodone. Strong CYP3A4 inhibitors, such as nefazodone, should be avoided in patients receiving ixabepilone.
Nefazodone	Maraviroc	The pharmacologic effects of maraviroc may be increased by nefazodone. A dosage adjustment is recommended for maraviroc during concomitant therapy with strong CYP3A4 inhibitors, such as nefazodone. Coadministration is contraindicated in patients with severe renal impairment.
Nefazodone	Mifepristone	Plasma concentrations and pharmacologic effects of mifepristone may be increased by nefazodone.
Nefazodone	Ruxolitinib	Plasma concentrations and pharmacologic effects of ruxolitinib may be increased by nefazodone. A

Generic Name(s)	Interaction	Mechanism
		dose reduction of ruxolitinib or avoidance of ruxolitinib is recommended in patients receiving nefazodone.
Nefazodone	Saxagliptin	Plasma concentrations and pharmacologic effects of saxagliptin may be increased by nefazodone.
Trazodone	SSRIs	Unexpected toxic effects may occur when trazodone and certain SSRIs are coadministered. The mechanism of this interaction is unknown.
Trazodone	Delavirdine	Plasma concentrations of trazodone may be increased when coadministered with delavirdine. Inhibition of CYP3A4 isoenzymes by delavirdine may decrease the metabolic elimination of trazodone.
Vilazodone	Cyproheptadine	Pharmacologic effects of may be decreased or reversed by cyproheptadine. Symptoms of depression may recur, because cyproheptadine may directly antagonize the serotonin receptor activity of vilazodone.
Vilazodone	Lithium	Coadministration of lithium and vilazodone may cause central nervous system toxicity, including serotonin syndrome. Serum lithium concentrations may be increased lithium and vilazodone may increase serotonergic neurotransmission.
Vilazodone	L-tryptophan	Both agents acutely increase central nervous system serotonin activity. Coadministration of these two agents could result in serotonin syndrome.
Vilazodone	NSAIDs	Toxic effects may be increased with concurrent administration of NSAIDs and vilazodone. The risk of upper gastrointestinal bleeding may be increased. The mechanism of this interaction is unknown.
Vilazodone	Salicylates	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of salicylates and vilazodone. The mechanism of this interaction is unknown.
Vilazodone	SNRIs	The potential exists for the occurrence of additive serotonergic activity. Inhibition of cytochrome P450 2D6 isoenzymes by vilazodone may decrease the metabolic elimination of SNRIs. The development of serotonin syndrome is possible when the combination of SNRIs and vilazodone are coadministered. In addition, plasma concentrations of SNRIs may be increased by vilazodone.
Vilazodone	Strong CYP3A4 inhibitors	Strong CYP3A4 inhibitors may decrease the metabolic elimination of vilazodone, increasing the plasma concentrations and pharmacological effects of vilazodone.
Vilazodone	St. John’s wort	Unexpected toxicity may occur when St. John's wort and vilazodone are coadministered. The mechanism of this is unknown.
Vortioxetine	CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine)	Pharmacologic effects of vortioxetine may be increased by CYP2D6 inhibitors.

Generic Name(s)	Interaction	Mechanism
Tricyclics and Other Norepinephrine-reuptake Inhibitors		
TCAs	MAOIs	Although the combination of MAOIs and TCAs may be useful for treating depression, severe, sometimes lethal, toxicity may occur. Mechanism of this interaction is unknown.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Mibefradil	Pharmacologic and toxic effects of certain TCAs may be enhanced by mibefradil due to its effect on oxidative metabolism of coadministered agents. Substantial dosage adjustment of TCA may be necessary during concurrent administration with mibefradil.
TCAs (amitriptyline, desipramine, imipramine)	Droperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when droperidol and certain TCAs are coadministered.
TCAs (doxepin, nortriptyline)	Arsenic	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when these TCAs and Arsenic are coadministered.
TCAs (amitriptyline, desipramine, imipramine)	Pimozide	Certain TCAs and pimozide may cause additive adverse effects when coadministered. Cardiovascular toxicity may occur due to additive QT-interval prolongation.
TCAs (doxepin, nortriptyline)	Toremifene	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when toremifene is coadministered with these TCAs.
TCAs (doxepin, nortriptyline)	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and these TCAs.
TCAs (amitriptyline-chlordiazepoxide)	Azole antifungals	Inhibition of cytochrome P450 3A4 isoenzymes by azole antifungals may decrease the metabolic elimination of chlordiazepoxide and amitriptyline, increasing the pharmacological effects and duration of action of chlordiazepoxide and amitriptyline.
TCAs (amitriptyline-chlordiazepoxide)	Clozapine	Delirium, sedation, sialorrhea, and ataxia may occur when amitriptyline-chlordiazepoxide and clozapine are coadministered. Severe orthostatic hypotension and respiratory depression may occur when clozapine combined with amitriptyline-chlordiazepoxide. The mechanism of this interaction is unknown. Clozapine and amitriptyline- chlordiazepoxide should not be started simultaneously.
TCAs (amitriptyline-chlordiazepoxide)	Sodium oxybate	Concurrent use of sodium oxybate and amitriptyline-chlordiazepoxide may result in an additive increase in sleep duration and central nervous system depression.
TCAs (clomipramine)	Methylene blue	Coadministration of clomipramine and methylene blue may increase the risk of central nervous system toxicity, including serotonin syndrome.
TCAs	Quinidine	Pharmacologic effects of nortriptyline may be

Generic Name(s)	Interaction	Mechanism
(nortriptyline)		increased by quinidine. Elevated plasma concentrations with toxicity characterized by QT prolongation including torsades de pointes may occur. Mechanism: Inhibition of CYP2D6 isoenzymes by quinidine may decrease the metabolic elimination of nortriptyline which may increase the risk for concentration-dependent prolongation of the QT interval.
TCAs	Tramadol	Increased risk of seizures may occur when tramadol and TCAs are coadministered.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Cimetidine	Therapeutic efficacy and frequency of side effects of TCAs may be altered by concurrent therapy with cimetidine.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Clonidine	The antihypertensive effects of clonidine may be decreased by TCAs. TCAs may worsen rebound reactions from abrupt clonidine withdrawal.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Fluconazole	Fluconazole may increase plasma concentrations and toxic effects of these TCAs.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Fluoxetine	The pharmacologic and toxic effects of TCAs may be increased by fluoxetine, despite reports of increased clinical efficacy.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Fluvoxamine	The pharmacologic and toxic effects of TCAs may be increased by fluvoxamine. Toxicity may result.

Generic Name(s)	Interaction	Mechanism
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Guanfacine	The antihypertensive effect of guanfacine may be decreased by TCAs.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Iobenguane	TCAs may reduce uptake and diagnostic efficacy of iobenguane. False-negative iobenguane imaging tests may result.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Paroxetine	The pharmacologic/toxic effects and plasma concentrations of TCAs may be increased by paroxetine.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Rasagiline	The combination of rasagiline and these TCAs may precipitate symptoms of serotonin syndrome.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, protriptyline, trimipramine)	Sertraline	The pharmacologic and toxic effects of TCAs may be increased by sertraline.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)	Phenothiazines	Plasma concentrations of phenothiazines and TCAs may be increased when coadministered. Risk of toxicity associated with TCAs and/or risk for potential additive QT prolongation is possible with some when some TCAs are coadministered with phenothiazines.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine,	Carbamazepine	Serum carbamazepine levels may be elevated, increasing pharmacologic and toxic effects, while TCA levels may be decreased. Carbamazepine may alter the parent drug-hydroxylated metabolite ratio, resulting in increased risk of toxicity or loss of efficacy of TCAs.

Generic Name(s)	Interaction	Mechanism
nortriptyline)		
TCAs (amoxapine, clomipramine, desipramine,nortriptyline)	Abiraterone	Plasma concentrations and pharmacologic effects of these TCAs may be increased by abiraterone. Coadministration of these TCAs and abiraterone should be avoided.
TCAs (amitriptyline, desipramine, doxepin, imipramine, nortriptyline)	Duloxetine	Plasma concentrations of these TCAs may be increased by duloxetine. Serotonin syndrome is also a risk with this combination.
TCAs (amitriptyline, clomipramine, desipramine, imipramine, nortriptyline)	Terbinafine	The pharmacologic and toxic effects of TCAs may be increased by terbinafine. Toxic signs may occur.
TCAs (amitriptyline, clomipramine, nortriptyline)	Valproic acid and derivatives	Plasma concentrations and toxic effects of these TCAs may be increased by valproic acid and its derivatives.
TCAs (amitriptyline-chlordiazepoxide)	Hydantoins	Pharmacologic effects of hydantoins may be increased by amitriptyline-chlordiazepoxide. Elevated hydantoin plasma concentrations and toxicity may occur. Serum concentrations and pharmacologic effects of amitriptyline-chlordiazepoxide may be decreased by hydantoins.
TCAs (amitriptyline-chlordiazepoxide)	Rifamycins	Pharmacologic effects of chlordiazepoxide-amitriptyline may be decreased by rifamycins.
TCAs (amitriptyline-chlordiazepoxide)	Disulfiram	Pharmacologic and toxic effects of amitriptyline-chlordiazepoxide may be increased by disulfiram. Disulfiram may inhibit hepatic metabolism of amitriptyline- chlordiazepoxide.
TCAs (amitriptyline-chlordiazepoxide)	Nefazodone	Nefazodone may increase the pharmacologic effects of amitriptyline-chlordiazepoxide. Impaired psychomotor performance and increased sedation may result from elevated amitriptyline-chlordiazepoxide plasma concentrations.
Antidepressants, Miscellaneous		
Brexanolone, esketamine	CNS depressants	Concomitant use of brexanolone or esketamine with CNS depressants (e.g., opioids, benzodiazepines, alcohol) may increase the likelihood or severity of adverse reactions related to sedation.
Bupropion	MAOIs	The use of bupropion with MAOIs is contraindicated due to the potential for hypertensive crisis. Only very high doses of selegiline participate in this interaction.
Bupropion	Linezolid	Manufacturer's literature states that the use of bupropion with linezolid is contraindicated due to risk for hypertensive crisis.
Bupropion	Methylene blue	Coadministration of bupropion and methylene blue may increase the risk of hypertensive

Generic Name(s)	Interaction	Mechanism
		reactions. The official package labeling of bupropion contraindicates the initiation of bupropion in patients receiving methylene blue.
Bupropion	Pimozide	Plasma concentrations of pimozide may be increased by bupropion. Coadministration of pimozide with bupropion is contraindicated.
Bupropion	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by bupropion. Coadministration of bupropion with tamoxifen may increase the risk of breast cancer recurrence.
Dextromethorphan	Strong Inhibitors of CYP2D6	Concomitant use with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan. Dosage adjustment is necessary.
Dextromethorphan	Strong Inducers of CYP2B6	Concomitant use with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of dextromethorphan-bupropion. Avoid co-administration with strong inducers of CYP2B6.
Dextromethorphan and bupropion	Drugs Metabolized by CYP2D6	Coadministration of dextromethorphan-bupropion with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6.
Dextromethorphan and bupropion	Digoxin	Coadministration of dextromethorphan-bupropion with digoxin may decrease plasma digoxin levels. Monitor plasma digoxin levels in patients treated concomitantly with dextromethorphan-bupropion and digoxin.
Esketamine	MAOIs	Concomitant use with MAOIs may increase blood pressure. Closely monitor blood pressure with concomitant use of esketamine with MAOIs.
Esketamine	Psychostimulants	Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of esketamine with psychostimulants.
Mirtazapine	MAOIs	Concomitant administration of mirtazapine and MAOIs may enhance the sympathomimetic effects of mirtazapine. Concomitant use of mirtazapine and MAOIs is contraindicated. Only higher doses of selegiline participate in this interaction.
Mirtazapine	Furazolidone	Concomitant administration of mirtazapine and furazolidone may enhance the sympathomimetic effects of mirtazapine. The mechanism is unknown.
Mirtazapine	Linezolid	Coadministration of mirtazapine and linezolid may increase the risk of central nervous system toxicity, including serotonin syndrome. Coadministration of mirtazapine and linezolid is contraindicated. The initiation of mirtazapine is contraindicated in patients receiving linezolid according to the package labeling of mirtazapine.
Mirtazapine	Methylene blue	Coadministration of mirtazapine and methylene blue may increase the risk of central nervous

Generic Name(s)	Interaction	Mechanism
		system toxicity, including serotonin syndrome. The official package labeling of mirtazapine contraindicates the initiation of mirtazapine in patients receiving methylene blue.
Mirtazapine	Perampanel	The central nervous system effects of mirtazapine may be enhanced by perampanel. In addition, increased levels of confusion, depression, anger and aggression may occur.
Bupropion	Lopinavir/ritonavir	Plasma concentrations and pharmacologic effects of bupropion may be decreased by lopinavir/ritonavir.
Bupropion	Rifamycins	Bupropion plasma concentrations may be reduced secondary to increased metabolism of bupropion. In patients receiving bupropion, close monitoring of clinical efficacy is advised when rifamycins is coadministered.
Bupropion	Ritonavir	Plasma concentrations and pharmacologic effects of bupropion may be decreased by ritonavir.
Bupropion	Tiagabine	The potential exists for seizures to occur in patients receiving tiagabine who are also receiving drugs such as bupropion that are known to lower the seizure threshold.
Mirtazapine	Hydantoins	Mirtazapine plasma concentrations may be reduced by hydantoins.

CNS=central nervous system, COMT=catechol-O-methyltransferase, HIV=human immunodeficiency virus, MAOI=monoamine oxidase inhibitors, MTOR=mammalian target of rapamycin, NSAIDS=nonsteroidal anti-inflammatory drugs, SNRI=serotonin–norepinephrine reuptake inhibitors, SSRI=selective serotonin re-uptake inhibitors, TCA=tricyclic antidepressants

VI. Adverse Drug Events

The most common adverse drug events reported with the antidepressants are listed in Tables 6a to 6f. The boxed warnings for the antidepressants are listed in Tables 7 to 12.

Table 6a. Adverse Drug Events (%) Reported with the Monoamine Oxidase Inhibitors[1-3]

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Cardiovascular				
Arrhythmia	-	-	<1	-
Atrial fibrillation	-	-	<1	-
Bradycardia	-	-	<1	-
Cardiovascular depression	-	✔	-	-
Chest pain	-	-	≥1	-
Hypertension	-	-	≥1	-
Hypotension	-	-	3 to 10	-
Myocardial infarct	-	-	<1	-
Orthostatic hypotension	4	✔	-	✔
Palpitation	2	-	<1	✔
Peripheral edema	-	-	≥1	-
Peripheral vascular disorder	-	-	<1	-
Postural hypotension	-	✔	-	-
Syncope	2	-	<1	-
Tachycardia	-	✔	<1	✔
Vasodilation	-	-	<1	-
Central Nervous System				

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Abnormal thinking	-	-	>1	-
Agitation	-	-	>1	✔
Akathisia	✔	-	-	-
Akinesia	-	-	-	✔
Amnesia	-	-	>1	-
Anxiety	2	✔	-	✔
Ataxia	✔	✔	<1	✔
Behavior changes	-	-	>1	-
Bradykinesia	-	-	>1	-
Coma	✔	✔	-	-
Confusion	-	-	<1	✔
Convulsions	-	✔	-	-
Delirium	-	✔	-	-
Delusions	-	-	<1	-
Depersonalization	-	-	<1	-
Depression	-	-	<1	-
Disorientation	-	-	-	✔
Dizziness	15 to 29	✔	-	✔
Drowsiness	4	✔	-	✔
Emotional lability	-	-	<1	-
Euphoria	✔	✔	<1	-
Fatigue	-	✔	-	✔
Forgetfulness	2	-	-	-
Hallucinations	<1	-	-	-
Headache	6 to 15	✔	18	✔
Hostility	-	-	<1	-
Hyperactivity	2	-	-	-
Hyperesthesia	-	-	<1	-
Hyperkinesias	-	-	<1	-
Hyperreflexia	-	✔	-	✔
Hypersomnia	-	✔	-	-
Insomnia	4 to 6	✔	12	✔
Jitteriness	-	✔	-	-
Lethargy	2	-	-	-
Loss of balance	-	-	<1	-
Manic symptoms	-	✔	<1	✔
Migraine	-	-	<1	-
Neuritis	✔	-	-	-
Neurosis	-	-	<1	-
Numbness	-	-	-	✔
Palilalia	-	✔	-	-
Paranoid reaction	-	-	<1	-
Parasomnia	-	-	>1	-
Paresthesia	2	✔	>1	✔
Restlessness	-	-	-	✔
Schizophrenia precipitation	-	✔	-	-
Sedation	2	-	-	-
Seizure	-	✔	-	-
Sleep disturbance	2 to 5	✔	-	✔
Tremor	4	✔	<1	✔
Twitching	-	✔	<1	✔
Vertigo	-	-	<1	-
Weakness	-	✔	-	✔
Dermatological				

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Acne	-	-	≥1	-
Alopecia	-	-	<1	✔
Application site reaction	-	-	24	-
Bruising	-	-	≥1	-
Cystic acne flare-up	-	-	-	✔
Maculopapular rash	-	-	<1	-
Photosensitivity	✔	-	<1	-
Pruritus	-	✔	≥1	✔
Rash	-	✔	4	✔
Scleroderma	-	-	-	✔
Skin benign neoplasm	-	-	<1	-
Skin hypertrophy	-	-	<1	-
Urticaria	-	-	<1	✔
Vesiculobullous rash	-	-	<1	-
Gastrointestinal				
Abdominal pain	-	-	-	✔
Anorexia	-	-	≥1	✔
Appetite increased	-	-	<1	-
Black tongue	✔	-	-	-
Colitis	-	-	<1	-
Constipation	4 to 7	✔	>11	✔
Dental caries	-	-	<1	-
Diarrhea	2	-	9	✔
Dyspepsia	-	-	4	-
Eructation	-	-	<1	-
Flatulence	≥1	-	≥1	-
Gastritis	<1	-	<1	-
Gastroenteritis	≥1	-	≥1	-
Gastrointestinal disturbances	-	✔	-	-
Melena	<1	-	<1	-
Nausea	4 to 6	✔	-	✔
Rectal hemorrhage	<1	-	<1	-
Salivation increased	-	-	<1	-
Taste perversion	-	-	≥1	-
Tongue edema	-	-	<1	-
Vomiting	≥1	✔	≥1	-
Weight gain	-	✔	-	-
Weight loss	-	-	5	-
Xerostomia	6 to 9	✔	8	✔
Genitourinary				
Anorgasmia	-	✔	-	-
Cystitis	-	-	<1	-
Dysmenorrhea	-	-	≤1	-
Dysuria	✔	-	<1	-
Ejaculation disturbances	-	✔	-	✔
Hematuria	-	-	<1	-
Impotence	2	✔	-	✔
Incontinence	✔	-	-	-
Kidney calculus	-	-	<1	-
Libido increased	-	-	<1	-
Menorrhagia	-	-	<1	-
Pelvic pain	-	-	<1	-
Polyuria	-	-	<1	-
Prostatic hyperplasia	-	-	<1	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Sexual disturbances	✔	✔	≤1	-
Urinary frequency	2	-	<1	✔
Urinary hesitancy	1	-	-	-
Urinary retention	✔	✔	<1	✔
Urinary tract infection	-	-	≥1	-
Urinary urgency	-	-	<1	-
Urination impaired	-	-	<1	-
Vaginal hemorrhage	-	-	<1	-
Vaginal moniliasis	-	-	<1	-
Hematologic				
Agranulocytosis	-	-	-	✔
Anemia	-	-	<1	✔
Hematologic changes	✔	-	-	-
Leukocytosis	-	-	<1	-
Leukopenia	-	✔	<1	✔
Thrombocytopenia	-	-	-	✔
Hepatic				
Hepatitis	-	✔ -	-	✔
Jaundice	-	✔	-	-
Liver function tests abnormal	-	-	<1	-
Hepatocellular damage	-	✔	-	-
Transaminases increased	-	✔	-	-
Laboratory Test Abnormalities				
Alkaline phosphatase increased	-	-	<1	-
Hypercholesterolemia	-	-	<1	-
Hyperglycemia	-	-	<1	-
Hypernatremia	-	✔	-	-
Hypoglycemic reaction	-	-	<1	-
Hyponatremia	-	-	<1	✔
Lactate dehydrogenase increased	-	-	<1	-
Musculoskeletal				
Generalized spasm	-	-	<1	-
Heavy feeling	2	✔	-	-
Hypertonia	-	-	<1	-
Myalgia	-	-	≥1	-
Myasthenia	-	-	<1	-
Myoclonic jerks/movements	2	✔	<1	✔
Neck pain	-	-	≥1	-
Tenosynovitis	-	-	<1	-
Respiratory				
Asthma	-	-	<1	-
Bronchitis	-	-	≥1	-
Cough	-	-	≥1	-
Dyspnea	-	-	<1	-
Laryngismus	-	-	<1	-
Pharyngitis	-	-	3	-
Pneumonia	-	-	<1	-
Respiratory depression	-	✔	-	-
Sinusitis	-	-	3	-
Special Senses				
Blurred vision	✔	✔	-	✔
Glaucoma	-	✔	-	✔
Nystagmus	-	✔	-	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Tinnitus	-	-	<1	✔
Visual field defect	-	-	<1	-
Toxic amblyopia	✔	-	-	-
Other				
Bacterial infection	-	-	<1	-
Bilirubinemia	-	-	<1	-
Breast Pain	-	-	<1	-
Chills	2	-	<1	✔
Circumoral paresthesia	-	-	<1	-
Dehydration	-	-	<1	-
Diaphoresis	2	✔	≥1	✔
Edema	-	✔	<1	✔
Edema of the glottis	-	✔	-	-
Epistaxis	-	-	<1	-
Facial edema	-	-	<1	-
Fever	-	✔	<1	-
Fungal infection	-	-	<1	-
Glossitis	-	-	<1	-
Heat stroke	-	-	<1	-
Hernia	-	-	<1	-
Hypermetabolic syndrome	-	✔	-	✔
Impaired water secretion	✔	-	-	✔
Lupus-like syndrome	-	✔	-	-
Lymphadenopathy	-	-	<1	-
Moniliasis	-	-	<1	-
Neoplasia	-	-	<1	-
Osteoporosis	-	-	<1	-
Otitis external	-	-	<1	-
Parasitic infection	-	-	<1	-
Periodontal abscess	-	-	<1	-
Syndrome of inappropriate antidiuretic hormone secretion	✔	✔	-	✔
Suicide attempt	-	-	<1	-
Sweating	2	✔	>1	-
Toxic delirium	-	✔	-	-
Viral infection	-	-	<1	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6b. Adverse Drug Events (%) Reported with the Selective Serotonin- and Norepinephrine-reuptake Inhibitors[1-3]

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Cardiovascular				
Aneurysm	-	-	-	<1
Angina pectoris	-	-	<2	<1
Arrhythmia	-	-	-	<1
Atrial fibrillation	-	<1	-	-
Atrioventricular block	-	-	-	<1
Bigeminy	-	-	-	<1
Blood pressure increase	1 to 2	-	3	-
Bradycardia	-	-	-	<1
Bundle branch block	-	<1	-	<1
Cardiovascular disorder	-	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Cerebral ischemia	-	-	-	<1
Chest pain	-	-	<2	2
Congestive heart failure	-	<1	-	<1
Coronary artery disease	-	-	-	<1
Edema	-	-	-	✔
Electrocardiogram abnormalities	-	-	-	<1
Extrasystoles	-	-	<2	<1
Heart arrest	-	-	-	<1
Heart rate increase	-	-	6	-
Hemorrhage	-	-	-	<1
Hypertension, dose related and dose independent	<1	-	3	3 to 13
Hypertensive crisis	-	<1	-	-
Hypotension	-	-	3	<1
Myocardial infarct	<2	<1	-	<1
Myocardial ischemia	<1	-	-	-
Orthostatic hypotension	<2	<1	10 to 12	-
Palpitation	≤3	1 to 2	5	3
Peripheral edema	-	<1	-	-
Postural hypotension	-	-	-	1
Syncope	<2	<1	<2	<1
Tachycardia	<1	<1	6	2
Vasodilation	-	-	-	3 to 4
Central Nervous System				
Abnormal dreams	2 to 3	2 to 3	-	3 to 7
Abnormal thinking	-	-	-	2
Agitation	-	5 to 6	<2	2 to 4
Aggression	-	<1	<2	-
Amnesia	-	-	-	✔
Anger	-	-	<2	-
Anxiety	3 to 5	3	-	5 to 6
Ataxia	-	<1	-	<1
Blurred vision	-	4	-	4 to 6
Bradykinesia	-	-	-	<1
Chills	-	-	-	3
Concentration decreased	≤1	-	-	-
Confusion	-	-	-	2
Deafness	-	-	-	<1
Delusions	-	-	-	<1
Dementia	-	-	-	<1
Depersonalization	<2	-	-	1
Depression	-	-	-	1 to 3
Diplopia	-	<1	-	-
Disorientation	-	<1	-	-
Dizziness	10 to 13	6 to 17	-	11 to 20
Dystonia	-	-	-	<1
Extrapyramidal symptoms	<2	-	<2	-
Fatigue	7	2 to 15	-	-
Fever	-	1 to 3	-	✔
Guillain-Barre syndrome	-	-	-	<1
Hostility	-	-	-	<1
Hypoesthesia	-	1	-	-
Headache	-	13	-	25 to 38

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Hypoesthesia	-	1	-	✔
Hypomania	<2	-	-	-
Insomnia	9 to 12	8 to 6	-	15 to 23
Irritability	2	1	-	-
Lethargy	-	1	-	-
Loss of consciousness	-	-	-	<1
Mania	-	<1	-	-
Migraine	-	-	<2	✔
Mood swings	-	<1	-	-
Nervousness	-	1	-	6 to 21
Neuropathy	-	-	-	<1
Neutropenia	-	-	-	<1
Nightmares	-	1	-	-
Panic attack	-	-	<2	-
Paresthesia	≤2	1	<2	2 to 3
Parkinsonism	<1	-	-	-
Photopsia	-	<1	-	-
Photosensitivity	-	<1	-	-
Restlessness	-	1	-	-
Seizure	-	<1	-	<1
Sleep disorder	-	1	-	-
Somnolence	≤9	13 to 20	-	12 to 23
Tension	-	-	<2	-
Trismus	-	-	-	✔
Vertigo	-	1	-	✔
Yawning	-	1	<2	3 to 5
Dermatological				
Acne	-	<1	-	-
Alopecia	-	<1	-	-
Bruising	-	-	-	✔
Ecchymosis	-	<1	-	-
Eczema	-	<1	-	-
Erythema	-	<1	-	-
Erythema multiforme	-	-	-	<1
Exfoliative dermatitis	-	-	-	<1
Dry skin	-	-	<2	-
Hyperhidrosis	10 to 21	6 to 8	9	-
Maculopapular rash	-	-	-	<1
Miliaria	-	-	-	<1
Pruritus	-	3	<2	1
Rash	1	4	2	3
Skin atrophy	-	-	-	<1
Stevens-Johnson syndrome	-	<1	-	<1
Toxic epidermal necrolysis	-	-	-	<1
Urticaria	-	<1	<2	-
Endocrine and Metabolic				
Bilirubin increased	-	<1	-	<1
Blood urea nitrogen increased	-	-	-	<1
Cholesterol increased	3 to 4	<1	-	-
Creatinine increased	-	-	-	<1
Diabetes mellitus	-	-	-	<1
Dyslipidemia	-	<1	-	-
Electrolyte abnormalities	-	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Hepatic steatosis	-	<1	-	-
Hepatitis	-	<1	-	<1
Hot flushes	-	2	<2	-
Hypercalcinuria	-	-	-	<1
Hyperchlorhydria	-	-	-	<1
Hypercholesterolemia	-	<1	-	<15
Hyperglycemia	-	-	-	<1
Hyperkalemia	-	-	-	<1
Hyperlipidemia	-	<1	-	<1
Hyperphosphatemia	-	-	-	<1
Hyperthyroidism	-	-	-	<1
Hypertriglyceridemia	-	<1	-	-
Hyperuricemia	-	-	-	<1
Hypocholesterolemia	-	-	-	<1
Hypoglycemia	-	1	-	<1
Hypokalemia	-	-	-	<1
Hyponatremia	-	<1	-	<1
Hypophosphatemia	-	-	-	<1
Hypothyroidism	-	-	-	<1
Increased blood cholesterol	-	-	<2	-
Increased liver function tests	-	-	<2	-
Jaundice	-	<1	-	<1
Kidney function abnormal	-	-	-	<1
Low-density lipoprotein increased	≤1	-	-	-
Liver enzymes increased	≤2	-1	-	<1
Syndrome of inappropriate antidiuretic hormone secretion	-	<1	-	<1
Transaminase elevation	-	1	-	-
Triglycerides increased	-	-	-	✔
Weight gain	-	<1	-	✔
Weight loss	≤2	1 to 2	-	1 to 4
Gastrointestinal				
Abdominal pain	-	<1	<2	6
Abnormal taste	-	-	-	2
Anorexia	5 to 8	3 to 5	-	8 to 20
Aphthous stomatitis	-	<1	-	-
Appetite decreased	-	3 to 11	3	-
Appetite increased	-	-	-	✔
Bloody stools	-	<1	-	-
Cholelithiasis	-	-	-	<1
Colitis	-	<1	-	-
Constipation	9 to 11	5 to 15	9	8 to 15
Diarrhea	9 to 11	7 to 13	-	6 to 8
Diverticulitis	-	<1	-	-
Dyspepsia	-	4 to 5	-	7
Dysphagia	-	<1	-	-
Eructation	-	<1	-	-
Esophageal stenosis	-	<1	-	-
Flatulence	-	-	<2	3 to 4
Gastric emptying impaired	-	<1	-	-
Gastric irritation	-	<1	-	-
Gastric ulcer	-	<1	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Gastritis	-	1	-	-
Hematemesis	-	-	-	<1
Intestinal obstruction	-	-	-	<1
Irritable bowel syndrome	-	<1	-	-
Loose stools	-	2 to 3	-	-
Melena	-	<1	-	-
Nausea	22 to 26	14 to 30	17	21 to 58
Vomiting	≤4	1 to 6	5	3 to 6
Xerostomia	11 to 17	5 to 18	-	12 to 22
Genitourinary				
Crystalluria	-	-	-	<1
Dysuria	-	1	-	-
Ejaculation abnormality	≤1	1 to 4	5	2 to 19
Erectile dysfunction	3 to 6	1 to 5	6	-
Hematuria	-	-	<2	-
Impotence	-	-	-	4 to 10
Libido decreased	4 to 5	2 to 4	-	3 to 9
Menstrual abnormalities	-	-	-	<1
Micturition urgency	-	<1	-	-
Nocturia	-	<1	-	-
Pollakiuria	-	1 to 5	<2	-
Prostatic disorder	-	-	-	✔
Proteinuria	6 to 8	-	<2	-
Pyelonephritis	-	-	-	<1
Pyuria	-	-	-	<1
Testicular pain	-	-	4	-
Urinary frequency	-	-	-	3
Urinary hesitation	-	-	4	-
Urinary retention	-	<1	-	1
Urinary symptoms	≤1	1	-	-
Urination impaired	-	-	-	2
Hematologic				
Agranulocytosis	-	-	-	<1
Anemia	-	<1	-	-
Aplastic anemia	-	-	-	<1
Bleeding time increased	-	-	-	<1
Eosinophilia	-	-	-	<1
Hypoproteinemia	-	-	-	<1
Leukocytosis	-	-	-	<1
Leukoderma	-	-	-	<1
Leukopenia	-	<1	-	<1
Lymphadenopathy	-	<1	-	<1
Lymphocytosis	-	-	-	<1
Pancytopenia	-	-	-	<1
Thrombocytopenia	-	<1	-	<1
Thrombophlebitis	-	-	-	<1
Musculoskeletal				
Arthralgia	-	-	-	✔
Dysarthria	-	<1	-	-
Extrapyramidal symptoms	-	-	<2	<1
Hypertonia	-	-	-	3
Malaise	-	<1	-	-
Muscle cramp	-	4 to 5	-	-
Muscle pain	-	1 to 5	-	-

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Muscle tightness	-	1	-	1 to 2
Muscle twitching	-	4	-	<1
Myalgia	-	1 to 3	-	-
Myasthenia	-	-	-	<1
Myopathy	-	-	-	<1
Neck pain/rigidity	-	-	-	✔
Neuroleptic malignant-like syndrome	-	-	-	<1
Osteoporosis	-	-	-	<1
Rhabdomyolysis	-	-	-	<1
Rheumatoid arthritis	-	-	-	<1
Rigors	-	1	-	-
Tendon rupture	-	-	-	<1
Tremor	≤3	3 to 4	-	4 to 10
Weakness	≤2	2 to 8	-	8 to 19
Respiratory				
Asthma	-	-	-	<1
Atelectasis	-	-	-	<1
Cough	-	3 to 6	-	✔
Dyspnea	-	-	-	✔
Epistaxis	<2	-	-	-
Nasopharyngitis	-	7 to 9	-	-
Pharyngitis	-	-	-	7
Pharyngolaryngeal pain	-	1 to 6	-	-
Pleurisy	-	-	-	<1
Pneumonia	-	-	-	<1
Sinusitis	-	-	-	2
Upper respiratory infection	-	7	-	-
Other				
Anaphylactic reaction	-	<1	-	<1
Angioneurotic edema	-	<1	-	-
Arteritis	-	-	-	<1
Bacteremia	-	-	-	<1
Basophilia	-	-	-	<1
Blurred/abnormal vision	-	1 to 3	<2	4 to 6
Bruxism	-	<1	<2	-
Cataract	-	-	-	<1
Catatonia	-	-	-	<1
Cellulites	-	-	-	<1
Conjunctival hemorrhage	-	-	<2	-
Cyanosis	-	-	-	<1
Deep vein thrombosis	-	-	-	<1
Dehydration	-	<1	-	<1
Diaphoresis increased	10 to 14	6	-	10 to 14
Embolus	-	-	-	<1
Facial edema	-	<1	-	-
Facial paralysis	-	-	-	<1
Fasciitis	-	-	-	<1
Flu-like syndrome	-	<1	-	6
Gingivitis	-	<1	-	-
Glaucoma	-	<1	-	<1
Homicidal ideation	-	-	-	<1
Hot flushes	-	2 to 3	<2	-
Hyperacusis	-	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Hypersensitivity reaction	<2	-	-	-
Infection	-	-	-	6
Keratoconjunctivitis sicca	-	<1	-	-
Larynx edema	-	-	-	<1
Macular degeneration	-	<1	-	-
Maculopathy	-	<1	-	-
Moniliasis	-	-	-	<1
Multiple myeloma	-	-	-	<1
Mydriasis	2	-	-	2
Nephropathy	-	<1	-	-
Night sweats	-	1	-	-
Oropharyngeal edema	-	<1	-	-
Phlebitis	-	<1	-	-
Retinal detachment	-	<1	-	-
Serotonin syndrome	-	-	-	<1
Stomatitis	-	<1	-	-
Suicidal ideation/attempt	-	<1	-	<1 to 2
Thirst	-	<1	<2	-
Tinnitus	2	-	-	2
Trauma	-	-	-	2
Trismus	-	-	-	✔
Visual disturbance	-	<1	-	-
Withdrawal syndrome	-	<1	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6c. Adverse Drug Events (%) Reported with the Selective Serotonin-reuptake Inhibitors[1-3]

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Cardiovascular						
Angina	-	-	<1	<1	<1	-
Arrhythmia	-	-	<1	-	-	-
Atrial arrhythmia	-	-	-	-	<1	<1
Atrial fibrillation	-	<1	<1	-	-	-
Atrioventricular block	-	-	-	<1	-	<1
Bradycardia	1 to 10	<1	-	<1	<1	<1
Cardiomyopathy	-	-	-	<1	-	-
Cerebrovascular accident	-	<1	<1	<1	<1	-
Chest pain	<1	<1	>1	3	3	>1
Chest tightness	-	<1	-	-	<1	-
Congestive heart failure	-	-	<1	<1	<1	-
Coronary artery disease	-	-	-	<1	-	-
Electrocardiogram abnormal	-	<1	-	<1	-	-
Edema	<1	<1	<1	≤1	-	<1
Hemorrhage	-	-	✔	<1	-	-
Hypertension	<1	<1	>1	1 to 2	≥1	<1
Myocardial infarct	-	-	<1	<1	<1	-
Orthostatic hypotension	-	<1	-	≤1	<1	-
Palpitation	-	<1	>1	3	2 to 3	>1
Pericarditis	-	-	-	<1	-	-
Peripheral edema	-	-	<1	-	-	<1
Postural hypotension	1 to 10	-	<1	-	<1	<1
Pulmonary hypertension	-	-	<1	-	-	<1
QT_c prolongation	<1	<1	<1	-	-	<1
Supraventricular extrasystoles	-	-	-	<1	-	-
Syncope	-	<1	<1	≤1	<1	<1
Tachycardia	1 to 10	<1	<1	≤1	≥1	-
Vasculitis	-	<1	<1	<1	<1	<1
Vasodilation	-	-	1 to 5	2	2 to 4	-
Ventricular arrhythmia	<1	<1	-	-	<1	-
Ventricular tachycardia	<1	<1	<1	<1	<1	<1
Central Nervous System						
Abnormal dreams	-	3	1 to 5	3	3 to 4	<1
Abnormal gait	-	<1	<1	-	-	<1
Abnormal thinking	-	-	2	3	<1	-

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Aggression	-	<1	-	-	-	<1
Agitation	3 to 10	<1	>1	2 to 3	3 to 5	5
Akathisia	-	<1	<1	-	-	-
Akinesia	-	-	-	<1	<1	-
Amnesia	>1	<1	>1	✔	2	<1
Anxiety	4	<1	6 to 15	5 to 8	5	4
Apathy	>1	<1	<1	1 to 3	-	<1
Aphasia	-	-	-	-	<1	-
Asthenia	-	-	-	14	-	>1
Ataxia	-	-	<1	<1	<1	<1
Auditory hallucination	-	<1	-	-	-	-
Blindness	-	-	-	-	-	<1
Blurred vision	-	1 to 10	-	-	-	-
Chills	-	-	>1	2	<1	-
Central nervous system stimulation	-	-	<1	2	-	-
Concentration impaired	✔	1 to 10	-	-	3 to 4	<1
Confusion	>1	<1	>1	<1	1	<1
Deafness	-	-	-	-	<1	-
Delirium	<1	<1	-	-	<1	-
Depersonalization	-	<1	<1	-	≤3	-
Depression	>1	<1	>1	2	-	<1
Dizziness	-	5	9	11 to 15	6 to 14	12
Dyskinesias	<1	<1	<1	<1	<1	-
Dystonia	-	-	-	<1	<1	<1
Emotional lability	-	<1	>1	-	>1	<1
Euphoria	-	-	<1	-	<1	<1
Excitability	-	<1	-	-	-	-
Extrapyramidal symptoms	-	-	<1	<1	<1	<1
Fatigue	5	5 to 8	-	-	-	12
Fever	2	<1	2	-	-	-
Guillain-Barre syndrome	-	-	-	-	<1	-
Hallucinations	-	<1	<1	<1	<1	<1
Headache	-	24	21	22 to 35	17 to 18	25
Hiccup	-	-	<1	-	-	-
Hyperkinesia	-	-	<1	✔	-	<1
Hyperreflexia	-	<1	-	-	-	-
Hypertonia	-	-	<1	2	<1	>1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Hypoesthesia	-	<1	-	-	-	1 to 10
Hypokinesia	-	-	-	✔	-	<1
Hypomania	-	-	-	<1	-	-
Insomnia	>10	9 to 12	10 to 33	21 to 35	11 to 24	21
Irritability	-	<1	-	-	-	-
Lethargy	-	3	-	-	-	-
Lightheadedness	-	<1	-	-	-	-
Malaise	-	<1	<1	✔	-	1 to 10
Mania	-	-	-	✔	-	-
Meningitis	-	-	-	-	<1	-
Migraine	>1	<1	<1	-	<1	<1
Nervousness	-	-	8 to 14	10 to 12	4 to 9	5
Neuralgia	-	-	<1	<1	-	-
Neuropathy	-	-	<1	<1	<1	-
Neurosis	-	-	<1	2	<1	-
Nystagmus	-	<1	-	-	-	<1
Optic neuritis	-	-	<1	-	-	<1
Panic reaction	-	<1	-	-	-	-
Paralysis	-	-	-	<1	<1	-
Paresthesia	>1	2	-	3	4	2
Parkinsonism	-	<1	-	-	-	-
Psychiatric disturbances	-	<1	-	✔	-	<1
Seizure	-	✔	-	<1	<1	-
Somnolence	>10	6 to 13	5 to 17	22 to 27	15 to 24	13
Tardive dyskinesia	-	<1	-	<1	-	-
Tetany	-	-	-	-	<1	-
Tremors	8	-	9	4	-	8
Vertigo	-	<1	<1	-	>1	<1
Yawning	<10	2	<11	2 to 5	2 to 4	>1
Dermatological						
Acne	-	-	<1	2	<1	<1
Alopecia	-	-	<1	<1	<1	<1
Angioedema	-	-	-	<1	<1	<1
Bruising	-	-	<1	4	<1	-
Bullous eruption	-	-	-	<1	-	-
Cellulitis	-	-	-	-	<1	-
Ecchymosis	-	-	<1	2	<1	<1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Eczema	-	-	<1	<1	<1	<1
Epidermal necrolysis	<1	<1	<1	-	<1	-
Erythema multiforme	<1	<1	<1	-	<1	-
Erythema nodosum	>1	-	<1	-	-	-
Exfoliative dermatitis	>1	-	<1	-	<1	-
Photosensitivity	<1	-	<1	<1	<1	<1
Pruritus	✔	-	4	-	>1	<1
Rash	✔	<1	2 to 6	-	2 to 3	>10
Stevens-Johnson syndrome	-	-	<1	<1	-	<1
Urticaria	<1	-	-	<1	<1	<1
Endocrine and Metabolic						
Albuminuria	-	-	<1	-	-	-
Alkaline phosphatase increased	-	-	-	-	<1	-
Bilirubin increased	-	<1	-	-	<1	<1
Blood urea nitrogen increased	-	-	-	-	<1	-
Cholecystitis	-	-	-	<1	-	-
Cholelithiasis	-	-	<1	<1	<1	-
Cholestatic jaundice	-	-	<1	-	-	-
Diabetes mellitus	-	<1	-	-	<1	-
Galactorrhea	-	-	-	-	-	<1
Goiter	-	-	-	<1	<1	-
Gynecomastia	-	<1	<1	-	5	<1
Hepatic failure	-	-	<1	-	-	<1
Hepatic necrosis	<1	<1	<1	-	<1	-
Hepatitis	-	<1	-	<1	<1	<1
Hepatomegaly	-	-	-	-	-	<1
Hot flashes	-	<1	-	-	-	-
Hypercholesterolemia	-	<1	<1	<1	<1	-
Hyperglycemia	-	<1	-	<1	<1	<1
Hyperprolactinemia	-	-	<1	-	-	<1
Hyperthyroidism	-	-	-	-	<1	-
Hypoglycemia	-	<1	-	<1	<1	<1
Hypokalemia	-	<1	<1	<1	-	-
Hyponatremia	<1	-	<1	<1	-	-
Hypothyroidism	-	-	<1	<1	<1	<1
Jaundice	-	-	<1	<1	<1	<1
Syndrome of inappropriate antidiuretic hormone	<1	<1	-	-	-	<1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Transaminase elevation	-	-	-	-	<1	<1
Weight gain	>1	<1	>1	<1	>1	>1
Weight loss	>1	<1	2	1 to 2	<1	-
Gastrointestinal						
Abdominal cramps	-	1 to 10	-	-	-	-
Abdominal pain	3	2	-	5	4	<1
Abnormal taste	✔	<1	✔	2 to 3	2	-
Anorexia	4	-	4 to 17	6 to 14	5 to 9	6
Aphthous stomatitis	-	-	<1	-	<1	<1
Appetite decreased	-	3	-	4	5 to 9	-
Appetite increased	>1	1 to 10	✔	-	2 to 4	>1
Carbohydrate craving	-	<1	-	-	-	-
Cholelithiasis	-	-	<1	-	-	-
Colitis	-	-	<1	<1	<1	-
Constipation	-	3 to 5	5	4 to 10	5 to 16	6
Diarrhea	8	8	8 to 18	11 to 18	9 to 12	20
Dyspepsia	5	-	6 to 10	8 to 10	2 to 5	8
Dysphagia	-	<1	<1	2	<1	<1
Esophagitis	-	-	<1	-	-	<1
Flatulence	>1	2	3	4	4	1 to 10
Gastritis	-	-	<1	-	<1	-
Gastroenteritis	-	<1	<1	-	<1	<1
Gastrointestinal bleeding	-	-	-	<1	-	-
Gastrointestinal ulcer	-	-	<1	-	<1	-
Gingivitis	-	-	-	2	<1	-
Glossitis	-	-	<1	-	<1	-
Heartburn	-	<1	-	-	-	-
Hematemesis	-	-	-	<1	<1	-
Indigestion	-	3	-	10	-	-
Intestinal obstruction	-	-	-	<1	<1	-
Melena	-	-	<1	-	-	-
Nausea	>10	15	12 to 29	34 to 40	19 to 26	25
Pancreatitis	<1	<1	<1	<1	<1	<1
Vomiting	4	1 to 10	3	4 to 6	2 to 3	4
Xerostomia	>10	6 to 9	4 to 12	10 to 14	9 to 18	>10
Genitourinary						
Acute renal failure	<1	<1	<1	<1	<1	<1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Anorgasmia	-	2 to 6	2	2 to 5	2 to 9	-
Anuria	-	-	-	<1	-	-
Ejaculation disorder	6	9 to 14	<7	7 to 11	13 to 28	7 to 19
Hematuria	-	-	<1	<1	<1	<1
Impotence	3	2 to 3	<7	2	2 to 9	>1
Libido decreased	1 to 4	3 to 7	1 to 11	2 to 10	3 to 15	6
Menstrual cramps	-	1 to 10	-	-	-	-
Menstrual disorder	3	<1	<1 to 2	3	5	<1
Micturition disorders	✔	-	-	-	-	<1
Priapism	<1	<1	<1	-	-	<1
Sexual dysfunction	✔	-	-	2 to 4	-	>1
Urinary frequency	-	<1	✔	2 to 3	2 to 3	<1
Urinary incontinence	<1	-	<1	<1	<1	<1
Urinary retention	<1	-	<1	1	<1	<1
Urinary tract infection	-	<1	-	2	2	-
Hematologic						
Agranulocytosis	-	-	-	<1	-	<1
Anemia	-	<1	<1	<1	<1	-
Aplastic anemia	-	<1	<1	-	-	<1
Blood dyscrasias	-	-	-	-	<1	-
Hemolytic anemia	<1	<1	<1	-	-	-
Increased bleeding	-	-	-	-	<1	<1
Ketosis	-	-	-	-	<1	-
Leukocytosis	<1	-	-	<1	<1	-
Leukopenia	-	-	-	<1	<1	<1
Liver enzymes increased	<1	-	<1	1 to 2	<1	-
Lymphadenopathy	-	-	-	<1	<1	-
Pancytopenia	-	-	<1	-	<1	-
Platelet count abnormalities	-	-	-	-	<1	-
Porphyria	-	-	-	<1	-	-
Prothrombin decreased	-	<1	-	-	-	-
Purpura	<1	<1	<1	<1	-	>2
Thrombosis	-	<1	-	-	<1	-
Thrombocytopenia	-	<1	<1	<1	<1	<1
Thrombocytopenic purpura	-	-	<1	-	-	-
Musculoskeletal						
Arthralgia	2	<1	-	-	>1	<1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Arthritis	-	-	<1	-	<1	-
Back pain	-	-	-	-	3	>1
Bursitis	-	-	<1	-	-	-
Choreoathetosis	-	<1	-	-	-	-
Limb pain	-	1 to 10	-	-	-	-
Muscle contractions	-	<1	-	2	-	-
Muscle cramp	-	<1	<1	-	-	<1
Myalgia	2	<1	-	5 to 8	2 to 4	>1
Myoclonus	<1	-	-	-	2 to 3	-
Neck/shoulder pain	-	1 to 10	-	-	<1	-
Neuroleptic malignant syndrome	<1	<1	<1	<1	<1	<1
Osteoporosis	-	-	-	-	<1	-
Rhabdomyolysis	<1	<1	-	-	-	-
Rigors	<1	-	-	-	-	-
Tics	-	<1	-	-	-	-
Tremor	8	1 to 10	3 to 13	5 to 8	4 to 11	-
Weakness	-	<1	7 to 21	14 to 26	12 to 22	<1
Respiratory						
Asthma	-	-	<1	<1	<1	-
Bronchitis	-	<1	-	2	<1	<1
Cough	>1	1 to 10	-	✔	-	<1
Dyspnea	-	-	<1	2	<1	<1
Eosinophilic pneumonia	-	-	<1	-	-	-
Epistaxis	-	-	≥2	2	<1	<1
Hemoptysis	-	-	-	<1	<1	<1
Hyperventilation	-	-	<1	-	<1	<1
Laryngeal edema	-	-	<1	-	-	-
Laryngitis	-	-	-	3	-	<1
Laryngospasm	-	-	<1	-	-	-
Nasal congestion	-	1 to 10	-	-	-	-
Pharyngitis	-	-	3 to 11	6	4	-
Pulmonary embolism	-	<1	<1	<1	<1	-
Pulmonary fibrosis	-	-	<1	-	<1	-
Pulmonary hypertension	-	-	<1	-	<1	-
Respiratory infection	5	-	-	9	7	<1
Rhinitis	5	5	-	-	3	>1
Sinus headache	-	<1	-	-	-	-

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Sinusitis	3	3	1 to 6	✔	4	<1
Other						
Allergic reaction	-	<1	-	<1	>1	<1
Allergy	-	<1	<1	-	<1	-
Amblyopia	-	-	-	2 to 3	-	-
Anaphylaxis	<1	<1	<1	<1	<1	<1
Angioedema	<1	<1	-	-	-	-
Blindness	-	-	-	-	-	<1
Blurred/abnormal vision	-	<1	✔	<1	2 to 4	3
Cataract	-	-	<1	-	<1	<1
Dehydration	-	-	<1	-	<1	-
Diaphoresis	>10	4 to 5	2 to 8	6 to 7	5 to 14	4 to 6
Ear ache	-	<1	✔	-	-	-
Flu-like syndrome	-	5	3 to 10	3	-	-
Gout	-	-	<1	-	-	-
Gum hyperplasia	-	-	-	-	-	<1
Infection	-	-	-	-	5 to 6	-
Lupus-like syndrome	-	-	<1	-	-	<1
Oculogyric crisis	-	-	-	-	-	<1
Pain	-	-	<1	10	-	1 to 10
Retinal detachment	-	-	-	<1	-	-
Sepsis	-	-	-	-	<1	-
Serotonin syndrome	<1	<1	<1	<1	<1	<1
Serum sickness	-	-	-	-	-	<1
Spontaneous abortion	-	<1	-	-	-	-
Suicidal tendency	✔	<1	-	<1	<1	<1
Thirst	<1	<1	≥2	-	-	-
Tinnitus	-	<1	>1	-	>1	>1
Tooth disorder	-	2	-	2 to 3	-	-
Vasculitis	-	-	<1	-	-	-
Visual difficulty	-	<1	2	-	2 to 4	<1
Withdrawal syndrome	<1	<1	-	-	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6d. Adverse Drug Events (%) Reported with the Serotonin Modulators[1-3]

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Cardiovascular				
Atrioventricular block	<1	-	-	-
Bradycardia	1 to 10	<1	-	-
Edema	-	1 to 10	-	-
Hypertension	-	1 to 10	-	-
Hypotension	1 to 10	1 to 10	-	-
Palpitation	-	-	1 to 2	-
Peripheral edema	1 to 10	-	-	-
Postural hypotension	1 to 10	-	-	-
Syncope	-	1 to 10	-	-
Tachycardia	-	<1	-	-
Vasodilation	1 to 10	-	-	-
Ventricular extrasystoles	-	-	<1	-
Central Nervous System				
Abnormal dreams	1 to 10	-	3	<1 to 3
Agitation	>10	<1	-	-
Anxiety	-	<1	-	-
Ataxia	1 to 10	-	-	-
Chills	1 to 10	-	-	-
Concentration decreased	1 to 10	1 to 10	-	-
Confusion	1 to 10	1 to 10	-	-
Dizziness	>10	>10	6 to 8	6 to 9
Drowsiness	>10	>10	4 to 5	-
Fatigue	-	1 to 10	4	-
Fever	1 to 10	-	-	-
Hallucinations	<1	-	✔	-
Headache	>10	>10	15	-
Incoordination	1 to 10	1 to 10	-	-
Insomnia	>10	-	6 to 7	-
Lightheadedness	1 to 10	-	-	-
Mania	-	-	<1	-
Memory impairment	1 to 10	-	-	-
Panic attacks	-	-	<1	-
Paresthesia	1 to 10	-	3	-
Psychomotor retardation	1 to 10	-	-	-
Restlessness	-	-	3	-
Sedation	-	>10	>1	-
Seizure	<1	<1	-	-
Speech impairment	-	<1	-	-
Dermatological				
Alopecia	-	<1	-	-
Hyperhidrosis	-	-	≤1	-
Photosensitivity	<1	-	-	-
Pruritus	1 to 10	-	-	1 to 3
Rash	1 to 10	<1	✔	-
Stevens-Johnson syndrome	<1	-	-	-
Endocrine and Metabolic				
Galactorrhea	<1	-	-	-
Gynecomastia	<1	-	-	-
Hepatic failure	<1	-	-	-
Hepatic necrosis	<1	-	-	-
Hepatitis	<1	-	-	-
Hyponatremia	<1	-	✔	-

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Liver function tests abnormal	<1	-	-	-
Prolactin increased	<1	-	-	-
Weight gain	-	1 to 10	-	-
Weight loss	-	1 to 10	-	-
Gastrointestinal				
Abnormal taste	1 to 10	-	-	-
Appetite decreased	-	-	1 to 10	-
Appetite increased	1 to 10	-	2	-
Constipation	>10	1 to 10	-	3 to 6
Diarrhea	1 to 10	1 to 10	26 to 29	7 to 10
Dry mouth	-	-	-	6 to 8
Dyspepsia	1 to 10	-	3	-
Flatulence	-	-	3	1 to 3
Gastroenteritis	1 to 10	-	2	-
Nausea	>10	>10	22 to 24	21 to 32
Vomiting	1 to 10	>10	4 to 5	3 to 6
Xerostomia	>10	>10	7 to 8	7 to 8
Genitourinary				
Ejaculation delayed	-	-	1 to 2	-
Erectile dysfunction	-	-	2	-
Impotence	1 to 10	-	-	-
Libido decreased	1 to 10	-	3 to 5	-
Orgasm abnormal	-	-	2 to 4	-
Priapism	<1	<1	-	-
Sexual dysfunction	-	-	<2	≥10
Urinary frequency	1 to 10	-	-	-
Urinary retention	1 to 10	<1	-	-
Hematologic				
Hematocrit decreased	1 to 10	-	-	-
Leukopenia	<1	-	-	-
Thrombocytopenia	<1	-	-	-
Musculoskeletal				
Arthralgia	1 to 10	-	2	-
Extrapyramidal symptoms	-	<1	-	-
Hypertonia	1 to 10	-	-	-
Jittery	-	-	2	-
Myalgia	-	1 to 10	-	-
Neck rigidity	1 to 10	-	-	-
Rhabdomyolysis	<1	-	-	-
Tremor	1 to 10	1 to 10	2	-
Weakness	>10	-	-	-
Respiratory				
Bronchitis	1 to 10	-	-	-
Cough	1 to 10	-	-	-
Dyspnea	1 to 10	-	-	-
Nasal congestion	-	1 to 10	-	-
Pharyngitis	1 to 10	-	-	-
Other				
Abnormal feeling	-	-	<1	-
Abnormal taste	-	-	<1	-
Allergic reaction	<1	<1	-	-
Angioedema	<1	-	-	-
Blurred/abnormal vision	7 to 9	>10	≤1	-
Breast pain	1 to 10	-	-	-

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Cataracts	-	-	<1	-
Eye pain	1 to 10	-	-	-
Flu syndrome	1 to 10	-	-	-
Infection	1 to 10	-	-	-
Night sweats	-	-	≤1	-
Serotonin syndrome	<1	-	-	-
Thirst	1 to 10	-	-	-
Tinnitus	1 to 10	-	-	-
Visual field defect	1 to 10	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6e. Adverse Drug Events (%) Reported with the Tricyclics and Other Norepinephrine-reuptake Inhibitors[1-3]

Adverse Events	Single Entity Agents									Combination Products
	Amitriptyline	Amoxapine	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine	Amitriptyline-Chlordiazepoxide
Cardiovascular										
Aneurysm	-	-	<1	-	-	-	-	-	-	-
Arrhythmia	✔	✔	<1	✔	-	✔	✔	✔	✔	✔
Atrial flutter	-	-	<1	-	-	-	-	-	-	-
Atrioventricular conduction changes	✔	-	-	-	-	-	-	-	-	✔
Bradycardia	-	-	<1	-	-	-	-	-	-	-
Bundle branch block	-	-	<1	-	-	-	-	-	-	-
Cardiac arrest	-	-	<1	-	-	-	-	-	-	-
Cardiomyopathy	✔	-	-	-	-	-	-	-	-	✔
Cerebral hemorrhage	-	-	<1	-	-	-	-	-	-	-
Chest pain	-	-	4	-	-	-	-	-	-	-
Chills	-	-	2	-	-	-	-	-	-	-
Congestive heart failure	-	-	-	-	-	✔	-	-	-	-
Cyanosis	-	-	<1	-	-	-	-	-	-	-
Electrocardiogram changes	✔	1 to 7	<1	-	-	✔	-	-	-	✔
Edema	✔	1 to 7	3	✔	✔	-	✔	-	-	-
Encephalopathy	-	-	<1	-	-	-	-	-	-	-
Extrasystole	-	-	<1	-	-	-	-	-	-	-
Heart block	✔	✔	<1	-	-	✔	✔	✔	✔	✔
Hypertension	✔	<1	-	✔	✔	✔	✔	✔	✔	✔
Hypotension	✔	<1	1 to 10	✔	✔	-	✔	✔	✔	✔
Myocardial infarction	✔	✔	<1	✔	-	✔	✔	✔	✔	✔
Myocardial ischemia	-	-	<1	-	-	-	-	-	-	-
Orthostatic hypotension	✔	-	20	-	-	✔	✔	-	-	✔
Palpitations	✔	1 to 7	4	✔	-	✔	✔	✔	✔	✔
Peripheral ischemia	-	-	<1	-	-	-	-	-	-	-
Stroke	✔	✔	-	✔	-	✔	✔	✔	✔	✔
Syncope	✔	<1	>1	-	-	-	✔	-	-	✔
Tachycardia	✔	<1	4	✔	✔	✔	✔	✔	✔	✔
Vasospasm	-	-	<1	-	-	-	-	-	-	-
Central Nervous System										
Abnormal dreaming	-	-	3	-	-	-	-	-	-	-
Aggressiveness	-	-	2	-	-	-	-	-	-	-
Agitation	-	-	3	✔	-	✔	✔	✔	✔	-
Akathisia	-	-	-	-	-	-	-	-	-	1 to 10
Anxiety	✔	1 to 7	9	✔	-	✔	✔	✔	✔	✔
Aphasia	-	-	<1	-	-	-	-	-	-	-
Apraxia	-	-	<1	-	-	-	-	-	-	-
Ataxia	✔	1 to 7	<1	✔	✔	-	✔	✔	-	>10
Catalepsy	-	-	<1	-	-	-	-	-	-	-
Confusion	-	1 to 7	3	-	✔	-	✔	✔	-	1 to 10
Cognitive function (impaired)	✔	-	-	-	-	-	-	-	-	✔
Coma	✔	-	<1	-	-	-	-	-	-	✔

Adverse Events	Single Entity Agents									Combination Products
	Amitriptyline	Amoxapine	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine	Amitriptyline-Chlordiazepoxide
Confusion	✔	>1	3	✔	✔	✔	✔	-	✔	✔
Coordination impairment	✔	<1	5	✔	-	✔	✔	✔	✔	✔
Deafness	-	-	<1	-	-	-	-	-	-	-
Delirium	-	-	<1	✔	-	-	✔	✔	✔	-
Delusions	✔	✔	<1	-	-	✔	✔	✔	✔	✔
Depersonalization	-	-	2	-	-	-	-	-	-	-
Depression	-	-	5	-	<1	-	✔	-	-	-
Disinhibition	-	-	-	-	-	-	-	-	-	1 to 10
Disorientation	✔	<1	-	✔	✔	✔	✔	-	✔	✔
Dizziness	✔	1 to 7	54	✔	>1	✔	✔	✔	✔	✔
Drowsiness	✔	14	46 to 54	✔	✔	✔	✔	✔	✔	✔
Dysarthria	✔	-	-	-	-	-	-	-	-	>10
Dyskinesia	-	-	<1	-	-	-	-	-	-	-
Dysphagia	-	-	-	-	-	-	-	-	-	-
Dysphonia	-	-	<1	-	-	-	-	-	-	-
Dystonia	-	-	<1	-	-	-	-	-	-	-
Emotional lability	-	-	2	-	-	-	-	-	-	-
Euphoria	✔	-	-	-	-	-	-	-	-	✔
Excitement	✔	1 to 7	-	-	-	-	-	-	-	✔
Extrapyramidal symptoms	✔	<1	<1	✔	✔	✔	✔	✔	✔	✔
Fatigue	✔	1 to 7	35 to 39	✔	<1	✔	✔	✔	✔	✔
Fever	✔	<1	4	✔	-	-	✔	-	-	✔
Flushing	-	-	8	✔	<1	-	✔	-	✔	-
Hallucinations	✔	-	<1	✔	✔	✔	✔	✔	✔	✔
Hangover effect	-	-	-	-	-	-	-	✔	-	-
Headache	✔	1 to 7	52	✔	✔	✔	✔	-	✔	✔
Hemiparesis	-	-	<1	-	-	-	-	-	-	-
Hostility	-	-	<1	-	-	-	-	-	-	-
Hyperesthesia	-	-	<1	-	-	-	-	-	-	-
Hyperkinesia	-	-	<1	-	-	-	-	-	-	-
Hyperreflexia	-	-	<1	-	-	-	-	-	-	-
Hypertonia	-	-	4	-	-	-	-	-	-	-
Hypoesthesia	-	-	<1	-	-	-	-	-	-	-
Hypokinesia	-	-	<1	-	-	-	-	-	-	-
Hypomania	-	-	-	✔	-	-	✔	✔	-	-
Ideation	-	-	<1	-	-	-	-	-	-	-
Insomnia	✔	1 to 7	25	✔	-	✔	✔	✔	✔	✔
Irritability	-	-	2	-	-	-	-	-	-	-
Malaise	✔	-	>1	-	-	-	✔	-	✔	✔
Mania	-	-	<1	-	-	-	-	-	-	-
Memory impairment	-	-	9	-	-	-	-	-	-	-
Migraine	-	-	3	-	-	-	-	-	-	-
Nervousness	-	1 to 7	18	✔	-	-	-	-	✔	-
Neuralgia	-	-	<1	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents									Combination Products
	Amitriptyline	Amoxapine	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine	Amitriptyline-Chlordiazepoxide
Neuropathy	-	-	<1	-	-	-	-	-	-	-
Nightmares	✔	1 to 7	-	-	-	✔	✔	✔	✔	✔
Oculogyric crisis	-	-	<1	-	-	-	-	-	-	-
Oculomotor nerve paralysis	-	-	<1	-	-	-	-	-	-	-
Panic	-	-	1	-	-	-	✔	✔	-	-
Paranoia	-	-	<1	-	-	-	-	-	-	-
Paresis	-	-	9	-	-	-	-	-	-	-
Paresthesia	-	-	2	-	-	-	-	-	-	-
Parkinsonian syndrome	-	-	-	✔	-	-	-	-	-	-
Psychosis exacerbation	-	-	<1	✔	-	✔	✔	✔	✔	-
Psychosomatic disorder	-	-	3	-	-	-	-	-	-	-
Restlessness	✔	1 to 7	-	✔	-	✔	✔	✔	✔	✔
Sedation	✔	-	-	-	-	-	-	-	-	✔
Sensory disturbance	-	-	<1	-	-	-	-	-	-	-
Seizure	✔	<1	<1	✔	✔	✔	✔	✔	✔	✔
Somnolence	✔	-	-	-	-	-	-	-	-	✔
Sleep Disorder	-	-	4	-	-	-	-	-	-	-
Speech disorder	-	-	3	-	-	-	-	-	-	-
Stupor	-	-	<1	-	-	-	-	-	-	-
Syncope	-	<1	-	-	-	-	-	-	-	-
Twitching	-	-	7	-	-	-	-	-	-	-
Yawning	-	-	3	-	-	-	-	-	-	-
Dermatological										
Acne	-	-	2	-	-	-	-	-	-	-
Alopecia	✔	-	<1	✔	✔	<1	✔	✔	✔	✔
Cellulitis	-	-	<1	-	-	-	-	-	-	-
Cheilitis	-	-	<1	-	-	-	-	-	-	-
Dermatitis	-	-	2	-	-	-	-	-	-	-
Dry skin	-	-	2	-	-	-	-	-	-	-
Petechiae	-	-	-	✔	-	<1	✔	✔	✔	-
Photosensitivity	✔	<1	<1	✔	✔	<1	✔	✔	✔	✔
Pruritus	-	<1	6	✔	✔	<1	✔	✔	✔	✔
Rash	✔	1 to 7	8	✔	✔	<1	✔	✔	✔	✔
Skin discoloration	-	-	<1	-	-	-	-	-	-	-
Skin ulceration	-	-	<1	-	-	-	-	-	-	-
Urticaria	✔	<1	1	✔	-	<1	✔	✔	✔	✔
Endocrine and Metabolic										
Breast enlargement	✔	-	2	✔	✔	✔	✔	✔	✔	✔
Breast pain	-	-	1	-	-	-	-	-	-	-
Diabetes mellitus	-	-	<1	-	-	-	-	-	-	-
Galactorrhea	✔	<1	<1	✔	✔	✔	✔	✔	✔	✔
Goiter	-	-	<1	-	-	-	-	-	-	-
Glycosuria	-	-	<1	-	-	-	-	-	-	-
Gynecomastia	✔	-	<1	-	-	✔	✔	✔	-	✔

Adverse Events	Single Entity Agents									Combination Products
	Amitriptyline	Amoxapine	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine	Amitriptyline-Chlordiazepoxide
Hyperglycemia	✔	-	<1	✔	✔	✔	✔	-	✔	✔
Hypoglycemia	✔	-	-	✔	✔	✔	-	-	✔	✔
Lactation	-	-	4	-	-	-	-	-	-	-
Prolactin levels increased	-	1 to 7	-	-	-	-	-	-	-	-
Syndrome of inappropriate antidiuretic hormone secretion	✔	<1	<1	✔	✔	✔	✔	✔	✔	✔
Thirst	-	-	2	-	-	-	-	-	-	-
Gastrointestinal										
Abdominal pain/cramps	-	<1	11	✔	<1	✔	✔	-	✔	-
Anorexia	✔	-	12	✔	✔	✔	✔	✔	✔	✔
Appetite decreased	-	-	11	-	<1	-	✔	-	-	✔
Appetite increased	-	1 to 7	11	-	<1	-	✔	✔	✔	✔
Black tongue	✔	✔	-	✔	-	✔	✔	-	✔	✔
Blood in stool	-	-	<1	-	-	-	-	-	-	-
Chronic enteritis	-	-	<1	-	-	-	-	-	-	-
Constipation	✔	12	47	✔	<1	✔	✔	✔	✔	✔
Diarrhea	✔	<1	13	✔	✔	✔	✔	✔	✔	✔
Dysphagia	-	-	2	-	-	-	-	-	-	-
Dyspepsia	-	-	22	✔	<1	-	✔	-	-	-
Eructation	-	-	>1	-	-	-	-	-	-	-
Esophageal sphincter tone decrease	-	-	-	✔	✔	-	-	✔	✔	-
Esophagitis	-	-	1	-	-	-	-	-	-	-
Flatulence	-	<1	6	-	-	-	-	-	-	-
Gastric/peptic ulcer	-	-	<1	-	-	-	-	-	-	-
Indigestion	-	-	-	-	✔	-	-	✔	✔	-
Intestinal obstruction	-	-	<1	-	-	-	-	-	-	-
Irritable bowel syndrome	-	-	<1	-	-	-	-	-	-	-
Nausea	✔	1 to 7	33	✔	✔	✔	✔	✔	✔	✔
Paralytic ileus	✔	✔	<1	✔	-	✔	-	-	✔	✔
Reflux	-	-	<1	-	<1	-	✔	-	-	-
Salivation decreased	-	-	-	-	-	-	-	-	-	✔
Salivation increased	-	-	<1	-	-	-	-	-	-	✔
Stomatitis	✔	✔	>1	✔	✔	✔	-	-	✔	✔
Taste changes	✔	<1	8	✔	✔	✔	✔	✔	✔	✔
Tongue ulceration	-	-	<1	-	-	-	-	-	-	-
Vomiting	✔	<1	7	✔	<1	✔	✔	✔	✔	✔
Weight gain	✔	<1	18	✔	✔	✔	✔	✔	✔	✔
Weight loss	✔	<1	>1	✔	-	✔	✔	✔	✔	✔
Xerostomia	✔	14	84	✔	✔	✔	✔	✔	✔	✔
Genitourinary										
Albuminuria	-	-	<1	-	-	-	-	-	-	-
Cervical dysplasia	-	-	<1	-	-	-	-	-	-	-
Cystitis	-	-	2	-	-	-	-	-	-	-
Dysmenorrhea	-	-	12	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents									Combination Products
	Amitriptyline	Amoxapine	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine	Amitriptyline-Chlordiazepoxide
Dysuria	-	-	2	-	-	-	-	-	-	-
Ejaculation failure	-	-	42	-	-	-	-	-	-	-
Epididymitis	-	-	<1	-	-	-	-	-	-	-
Hematuria	-	-	<1	-	-	-	-	-	-	-
Impotence	✔	<1	20	✔	-	✔	✔	✔	✔	✔
Incontinence	-	-	<1	-	-	-	-	-	-	✔
Leucorrhea	-	-	2	-	-	-	-	-	-	-
Menstrual Disorder	-	-	4	-	-	-	-	-	-	-
Micturition disorder/difficulty	-	-	4 to 14	-	-	-	✔	✔	-	>10
Micturition frequency	-	-	5	-	-	-	-	-	-	-
Polyuria	-	-	-	✔	-	-	-	-	-	-
Pyelonephritis	-	-	<1	-	-	-	-	-	-	-
Renal calculus	-	-	<1	-	-	-	-	-	-	-
Renal cyst	-	-	<1	-	-	-	-	-	-	-
Sexual dysfunction	-	-	-	✔	-	-	✔	-	✔	✔
Testicular edema	✔	<1	-	✔	✔	✔	✔	✔	✔	-
Urinary retention	✔	<1	2	✔	✔	✔	✔	✔	✔	✔
Urinary tract infection	-	-	6	-	-	-	<1	-	-	-
Vaginal hemorrhage	-	-	<1	-	-	-	-	-	-	-
Vaginitis	-	-	2	-	-	-	-	-	-	-
Hematologic										
Agranulocytosis	✔	<1	-	✔	✔	<1	✔	✔	✔	✔
Aphasia	-	-	<1	-	-	-	-	-	-	-
Aphasia	-	-	<1	-	-	-	<1	-	-	-
Bone marrow depression	✔	-	<1	-	✔	-	✔	-	✔	✔
Eosinophilia	✔	-	-	✔	✔	<1	✔	✔	✔	✔
Hemoptysis	-	-	<1	-	-	-	-	-	-	-
Leukemoid reaction	-	-	<1	-	-	-	-	-	-	-
Leukopenia	✔	<1	-	-	✔	-	-	✔	-	✔
Lymphadenopathy	-	-	<1	-	-	-	-	-	-	-
Lymphoma-like disorder	-	-	<1	-	-	-	-	-	-	-
Purpura	✔	-	3	✔	✔	<1	✔	✔	✔	✔
Thrombocytopenia	-	-	-	✔	✔	<1	✔	✔	✔	-
Thrombophlebitis	-	-	<1	-	-	-	-	-	-	-
Hepatic										
Cholestatic jaundice	✔	-	-	✔	-	<1	✔	✔	✔	✔
Hepatitis	✔	<1	<1	✔	-	-	-	-	-	✔
Liver enzymes increased	✔	<1	-	✔	-	<1	✔	✔	✔	✔
Neuromuscular and skeletal										
Arthralgia	-	-	3	-	-	-	<1	-	-	-
Back pain	-	-	6	-	-	-	<1	-	-	-
Choreoathetosis	-	-	<1	-	-	-	-	-	-	-
Myalgia	-	-	13	-	-	-	<1	-	-	-
Myoclonus	-	-	13	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents									Combination Products
	Amitriptyline	Amoxapine	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine	Amitriptyline-Chlordiazepoxide
Myositis	-	-	<1	-	-	-	-	-	-	-
Neuroleptic malignant syndrome	✔	<1	-	-	-	-	-	-	-	✔
Numbness	✔	<1	-	✔	✔	✔	✔	✔	✔	✔
Paresthesia	✔	<1	1 to 10	✔	✔	✔	✔	-	✔	✔
Peripheral neuropathy	✔	-	-	✔	-	✔	✔	-	✔	✔
Tardive dyskinesia	✔	<1	-	-	✔	-	-	-	-	✔
Tingling	✔	<1	-	✔	-	✔	✔	✔	✔	✔
Torticollis	-	-	<1	-	-	-	-	-	-	-
Tremor	✔	1 to 7	54	✔	✔	✔	✔	✔	✔	✔
Weakness	✔	1 to 7	1	✔	✔	✔	-	✔	✔	✔
Ocular										
Abnormal Vision	-	-	18	-	-	-	-	-	-	-
Accommodation disturbances	✔	<1	<1	✔	-	✔	✔	-	✔	✔
Anisocoria	-	-	>1	-	-	-	-	-	-	-
Blepharitis	-	-	<1	-	-	-	-	-	-	-
Blepharospasm	-	-	>1	-	-	-	-	-	-	-
Blurred vision	✔	7	1 to 10	✔	<1	✔	✔	✔	✔	✔
Conjunctival hemorrhage	-	-	<1	-	-	-	-	-	-	-
Conjunctivitis	-	-	1	-	-	-	-	-	-	-
Exophthalmos	-	-	<1	-	-	-	-	-	-	-
Eye pain	-	-	1 to 10	-	-	-	✔	✔	✔	-
Glaucoma,	-	-	<1	-	-	-	-	-	-	-
Intraocular pressure increased	✔	<1	-	✔	-	-	-	✔	✔	✔
Keratitis	-	-	<1	-	-	-	-	-	-	-
Lacrimation abnormal	-	-	3	-	-	-	-	-	-	-
Mydriasis	✔	<1	2	✔	-	✔	✔	-	✔	✔
Ocular Allergy	-	-	>1	-	-	-	-	-	-	-
Scleritis	-	-	<1	-	-	-	-	-	-	-
Strabismus	-	-	<1	-	-	-	-	-	-	-
Otic										
Hyperacusis	-	-	<1	-	-	-	-	-	-	-
Tinnitus	✔	<1	6	✔	✔	✔	✔	✔	✔	1 to 10
Respiratory										
Bronchitis	-	-	<1	-	-	-	-	-	-	-
Bronchospasm	-	-	2	-	-	-	-	-	-	-
Cough	-	-	6	-	-	-	✔	-	-	-
Dyspnea	-	-	>1	-	-	-	-	-	-	-
Hypo/hyperventilation	-	-	<1	-	-	-	-	-	-	-
Epistaxis	-	-	2	-	-	-	-	-	-	-
Laryngitis	-	-	>1	-	-	-	-	-	-	-
Nasal congestion	-	<1	-	-	-	-	✔	-	-	✔
Pharyngitis	-	-	14	-	-	-	-	-	-	-
Pneumonia	-	-	<1	-	-	-	-	-	-	-
Rhinitis	-	-	12	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents									Combination Products
	Amitriptyline	Amoxapine	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine	Amitriptyline-Chlordiazepoxide
Sinusitis	-	-	6	-	-	-	✔	-	-	-
Other										
Allergic reactions	-	<1	3	✔	✔	-	✔	✔	✔	-
Dehydration	-	-	<1	-	-	-	-	-	-	-
Diaphoresis	✔	1 to 7	29	✔	✔	✔	✔	✔	-	✔
Diplopia	✔	-	<1	-	-	-	✔	-	-	✔
Endometrial hyperplasia	-	-	<1	-	-	-	-	-	-	-
Endometriosis	-	-	<1	-	-	-	-	-	-	-
Halitosis	-	-	>1	-	-	-	-	-	-	-
Ovarian cyst	-	-	<1	-	-	-	-	-	-	-
Pain	-	-	3	-	-	-	-	-	-	-
Parosmia	-	-	<1	-	-	-	-	-	-	-
Polyarteritis nodosa	-	-	<1	-	-	-	-	-	-	-
Serotonin syndrome	✔	-	-	-	-	-	-	-	-	✔
Suicide ideation/attempt	✔	-	<1	-	-	-	-	-	-	✔
Tooth caries	-	-	<1	-	-	-	-	-	-	-
Tooth disorder	-	-	5	-	-	-	-	-	-	-
Uterine hemorrhage	-	-	<1	-	-	-	-	-	-	-
Uterine inflammation	-	-	<1	-	-	-	-	-	-	-
Visual field defect	-	-	<1	-	-	-	-	-	-	-
Withdrawal reactions	✔	-	<1	-	-	-	-	-	-	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6f. Adverse Drug Events (%) Reported with the Antidepressants, Miscellaneous[1-3]

Adverse Events	Brexanolone	Bupropion	Dextromethorphan and Bupropion	Esketamine	Mirtazapine
Cardiovascular					
Arrhythmias	-	5	-	-	-
Atrioventricular block	-	✔	-	-	-
Chest pain	-	3 to 4	-	-	-
Electrocardiogram abnormality	-	✔	-	-	-
Extrasystoles	-	✔	-	-	-
Hypertension	-	2 to 4	-	10	2
Hypotension	-	3	-	-	-
Myocardial infarct	-	✔	-	-	<1
Orthostatic hypotension	-	-	-	-	<1
Palpitation	-	2 to 6	-	-	-
Peripheral edema	-	<1	-	-	2
Postural hypotension	-	✔	-	-	-
Stroke	-	✔	-	-	-
Syncope	-	✔	-	-	<1
Tachycardia	3	≤11	-	2	-
Vasodilation	-	✔	-	-	2
Central Nervous System					
Abnormal dreams	-	3	-	-	4
Abnormal thinking	-	-	-	-	3
Aggression	-	✔	-	-	-
Agitation	-	2 to 32	-	-	>
Akathisia	-	2	-	-	-
Akinesia	-	✔	-	-	-
Amnesia	-	✔	-	-	>1
Anxiety	-	5 to 7	4	13	>1
Aphasia	-	✔	-	-	-
Ataxia	-	✔	3	-	<1
Blurred vision	-	2 to 3	-	-	-
Central nervous system stimulation	-	1 to 2	-	-	-
Chills	-	<1	-	-	<1
Coma	-	✔	-	-	-
Confusion	-	8	-	-	2
Delirium	-	✔	-	-	<1
Delusions	-	✔	-	-	<1
Depersonalization	-	✔	-	-	<1
Depression	-	✔	-	-	-
Derealization	-	✔	-	-	-
Diplopia	-	✔	-	-	<1
Dissociation	-	-	-	41	-
Dizziness	12 to 13	6 to 22	14 to 16	29	7
Drowsiness	-	-	7	-	54
Dysarthria	-	-	-	4	-
Dysgeusia	-	-	-	19	-
Dyskinesia	-	✔	-	-	-
Dysphoria	-	✔	-	-	-
Dystonia	-	✔	-	-	<1
Emotional lability	-	✔	-	-	<1
Euphoria	-	✔	-	4	-
Fatigue	-	-	3	-	-
Fever	-	1 to 2	-	-	<1
Hallucinations	-	✔	-	-	<1
Headache	-	25 to 34	8	20	-
Hostility	-	6	-	-	<1
Hyperkinesia	-	✔	-	-	<1
Hypertonia	-	✔	-	-	-
Hypoesthesia	-	✔	-	18	-
Hypokinesia	-	✔	-	-	<1

Adverse Events	Brexanolone	Bupropion	Dextromethorphan and Bupropion	Esketamine	Mirtazapine
Hypomania	-	✔	-	-	-
Incoordination	-	✔	-	-	-
Insomnia	-	11 to 20	4	8	-
Irritability	-	2 to 3	-	-	-
Lethargy	-	-	-	11	-
Loss of consciousness	3 to 5	-	-	-	-
Malaise	-	✔	-	-	✔
Manic reaction	-	✔	-	-	<1
Memory decreased	-	<3	-	-	-
Mental impairment	-	-	-	3	-
Migraine	-	1 to 4	-	-	<1
Nervousness	-	3 to 5	-	-	-
Neuropathy	-	✔	-	-	-
Pain	-	2 to 3	-	-	-
Paranoia	-	✔	-	-	<1
Paresthesia	-	1 to 2	3	-	<1
Restlessness	-	✔	-	-	-
Seizure	-	✔	-	-	-
Sensory disturbance	-	4	-	-	-
Sleep disturbance	-	4	-	-	-
Somnolence	13 to 21	2 to 3	-	23	54
Vertigo	-	✔	-	23	-
Dermatological					
Hyperhidrosis	-	-	5	4	-
Maculopapular rash	-	✔	-	-	-
Photosensitivity	-	<1	-	-	<1
Pruritus	-	2 to 4	-	-	>1
Rash	-	1 to 5	-	-	>1
Urticaria	-	1 to 2	-	-	<1
Endocrine and Metabolic					
Appetite increased	-	4	-	-	17
Glycosuria	-	✔	-	-	-
Gynecomastia	-	✔	-	-	-
Hepatic damage	-	✔	-	-	-
Hepatitis	-	✔	-	-	-
Hypercholesterolemia	-	-	-	-	✔
Hyperglycemia	-	✔	-	-	-
Hypertriglyceridemia	-	-	-	-	✔
Hypoglycemia	-	✔	-	-	-
Hot flashes	-	1 to 3	-	-	-
Jaundice	-	<1	-	-	-
Liver function abnormal	-	<1	-	-	<1
Syndrome of inappropriate antidiuretic hormone	-	✔	-	-	-
Weight gain	-	-	-	-	12
Weight loss	-	14 to 23	-	-	<1
Gastrointestinal					
Abdominal pain	-	2 to 9	-	-	>1
Abnormal taste	-	2 to 4	-	-	-
Anorexia	-	3 to 5	-	-	>1
Appetite decreased	-	-	4	-	-
Colitis	-	✔	-	-	<1
Constipation	-	8 to 26	4	3	13
Diarrhea	2 to 3	5 to 7	7	7	-
Dry mouth	3 to 11	-	-	5	-
Dysphagia	-	<2	-	-	-
Dyspepsia	2	3	-	-	-
Flatulence	-	6	-	-	-
Gastric reflux	-	<1	-	-	-

Adverse Events	Brexanolone	Bupropion	Dextromethorphan and Bupropion	Esketamine	Mirtazapine
Gastrointestinal hemorrhage	-	✔	-	-	-
Intestinal perforation	-	✔	-	-	-
Nausea	-	1 to 18	13	28	<1
Oropharyngeal pain	2 to 3	-	-	-	-
Pancreatitis	-	✔	-	-	-
Stomach ulcer	-	✔	-	-	<1
Vomiting	-	2 to 4	-	9	>1
Xerostomia	-	10 to 28	6	-	25
Genitourinary					
Cystitis	-	✔	-	-	-
Dyspareunia	-	✔	-	-	-
Ejaculation abnormality	-	✔	-	-	-
Impotence	-	<1	-	-	<1
Libido decreased	-	3	-	-	-
Libido increased	-	✔	-	-	-
Menopause	-	✔	-	-	-
Menstrual complaints	-	2 to 5	-	-	<1
Painful erection	-	✔	-	-	-
Pollakiuria	-	-	-	3	-
Prostate disorder	-	✔	-	-	-
Salpingitis	-	✔	-	-	-
Sexual disorder	-	-	6	-	-
Urinary frequency	-	2 to 5	-	-	2
Urinary incontinence	-	✔	-	-	<1
Urinary retention	-	✔	-	-	<1
Urinary tract infection	-	<1	-	-	>1
Urinary urgency	-	<2	-	-	-
Vaginal hemorrhage	-	<2	-	-	-
Vaginitis	-	✔	-	-	>1
Hematologic					
Agranulocytosis	-	-	-	-	<1
Anemia	-	✔	-	-	-
Leukocytosis	-	✔	-	-	-
Leukopenia	-	✔	-	-	-
Neutropenia	-	-	-	-	<1
Pancytopenia	-	✔	-	-	-
Thrombocytopenia	-	✔	-	-	-
Musculoskeletal					
Arthralgia	-	1 to 4	3	-	2
Arthritis	-	2	-	-	-
Back pain	-	-	-	-	2
Dysarthria	-	✔	-	-	-
Extrapyramidal syndrome	-	✔	-	-	-
Musculoskeletal chest pain	-	✔	-	-	-
Myalgia	-	2 to 6	-	-	2
Neck pain	-	✔	-	-	<1
Rhabdomyolysis	-	✔	-	-	-
Rigidity	-	✔	-	-	-
Tardive dyskinesia	-	✔	-	-	-
Tremor	-	3 to 21	-	3	2
Twitching	-	1 to 2	-	-	<1
Weakness	-	2 to 4	-	-	8
Respiratory					
Bronchospasm	-	✔	-	-	-
Cough	-	1 to 4	-	-	-
Dyspnea	-	-	-	-	1
Nasal discomfort	-	-	-	7	-
Oropharyngeal pain	-	-	-	3	-
Pharyngitis	-	3 to 13	-	-	-

Adverse Events	Brexanolone	Bupropion	Dextromethorphan and Bupropion	Esketamine	Mirtazapine
Pneumonia	-	✔	-	-	-
Pulmonary embolism	-	✔	-	-	-
Sinusitis	-	1 to 5	-	-	-
Throat irritation	-	-	-	7	-
Upper respiratory infection	-	9	-	-	-
Other					
Accommodation abnormality	-	<1	-	-	<1
Allergic reaction	-	✔	-	-	-
Amblyopia	-	2	-	-	-
Angioedema	-	✔	-	-	-
Auditory disturbance	-	5	-	-	-
Bruxism	-	✔	-	-	-
Deafness	-	✔	-	-	<1
Dehydration	-	-	-	-	<1
Diaphoresis	-	5 to 22	-	-	-
Dry eye	-	✔	-	-	-
Ecchymosis	-	✔	-	-	-
Edema	-	-	-	-	1
Esophagitis	-	✔	-	-	-
Facial edema	-	✔	-	-	-
Feeling abnormal	-	-	-	3	-
Feeling drunk	-	-	-	5	-
Flu-like syndrome	-	-	-	-	1
Flushing	2 to 5	-	-	-	-
Gingivitis	-	✔	-	-	-
Glossitis	-	✔	-	-	-
Gum hemorrhage	-	✔	-	-	-
Hirsutism	-	✔	-	-	-
Hypersensitivity reactions	-	✔	-	-	-
Infection	-	8 to 9	-	-	-
Intraocular pressure increased	-	✔	-	-	-
Leg cramps	-	<1	-	-	-
Lymphadenopathy	-	✔	-	-	<1
Mouth ulcers	-	✔	-	-	-
Mydriasis	-	✔	-	-	-
Phlebitis	-	✔	-	-	-
Salivation increased	-	<1	-	-	<1
Sciatica	-	✔	-	-	-
Stomatitis	-	✔	-	-	-
Suicidal ideation	-	✔	✔	-	-
Thirst	-	<1	-	-	>1
Tinnitus	-	3 to 6	-	-	-
Tongue edema	-	✔	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 7. Boxed Warning for the Antidepressants[1]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of antidepressants in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared to placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Monitor patients of all ages who are started on antidepressant therapy appropriately and observe them

WARNING
closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Amitriptyline, amoxapine, bupropion, citalopram, dextromethorphan-bupropion, desipramine, desvenlafaxine, doxepin, esketamine, fluvoxamine (extended-release capsules), isocarboxazid, levomilnacipran, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, tranylcypromine, trazodone, trimipramine, venlafaxine, vilazodone, and vortioxetine are not approved for use in pediatric patients. Clomipramine, fluvoxamine, and sertraline are not approved for use in pediatric patients, except for patients with obsessive compulsive disorder. Escitalopram is not approved for use in children younger than 12 years of age. Fluoxetine (except Sarafem®) is approved for use in children with major depressive disorder (aged eight years and older) and obsessive-compulsive disorder (aged seven years and older). Imipramine is not approved for use in pediatric patients, except for patients with nocturnal enuresis. Selegiline is not approved for use in pediatric patients. Furthermore, selegiline at any dose should not be used in children younger than 12 years of age, even when administered with dietary modifications.

Table 8. Boxed Warning for Bupropion[1]

WARNING
Use in Smoking Cessation Treatment: Forfivo XL®, Wellbutrin®, Wellbutrin SR®, and Wellbutrin XL® are not approved for smoking cessation treatment, but bupropion under the name Zyban® is approved for this use. Although Zyban® is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications Wellbutrin®, Wellbutrin SR®, and Wellbutrin XL®. Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

Table 9. Boxed Warning for Nefazodone[1]

WARNING
Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The reported rate in the United States is approximately one case of liver failure resulting in death or transplant per 250,000 to 300,000 patient-years of nefazodone treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, one patient-year is equal to two patients each treated for six months, three patients each treated for four months, etc. Ordinarily, treatment with nefazodone should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that preexisting liver disease increases the likelihood of developing liver failure; however, baseline abnormalities can complicate patient monitoring. Advise patients to be alert for signs and symptoms of liver dysfunction (e.g., jaundice, anorexia, gastrointestinal complaints, malaise) and to report them to their health care provider immediately if they occur. Discontinue nefazodone if clinical signs or symptoms suggest liver failure. If nefazodone-treated patients develop evidence of hepatocellular injury such as increased serum aspartate aminotransferase or serum alanine aminotransferase levels greater than or equal to three times the upper limit of normal, withdraw the drug. These patients should be presumed to be at increased risk for liver injury if nefazodone is reintroduced. Accordingly, do not consider such patients for retreatment.

Table 10. Boxed Warning for Tranylcypromine[1]

WARNING
Hypertensive crisis with significant tyramine use: Excessive consumption of foods or beverages with significant tyramine content or the use of certain drugs with tranylcypromine or after tranylcypromine discontinuation can precipitate hypertensive crisis. Monitor blood pressure and allow for medication-free intervals between administration of tranylcypromine and interacting drugs. Instruct patients to avoid ingestion of foods and beverages with high tyramine content.

Table 11. Boxed Warning for Brexanolone[1]

WARNING
Excessive sedation and sudden loss of consciousness: Patients are at risk of excessive sedation or sudden loss of consciousness during administration of brexanolone. Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren). Because of these risks, brexanolone is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

Table 12. Boxed Warning for Esketamine[1]

WARNING
WARNING: Sedation; Dissociation; Respiratory Depression; Abuse And Misuse; And Suicidal Thoughts And Behaviors Sedation • Patients are at risk for sedation after administration of Spravato®. Dissociation • Patients are at risk for dissociative or perceptual changes after administration of Spravato®. Respiratory Depression • Respiratory depression has been observed in postmarketing experience. Because of the risks of sedation, dissociation, and respiratory depression, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. Abuse and Misuse • Spravato® has the potential to be abused and misused. Consider the risks and benefits of prescribing Spravato® prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. Because of the risks of serious adverse outcomes resulting from sedation, dissociation, respiratory depression, abuse and misuse, Spravato® is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS. Suicidal Thoughts and Behaviors Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. Spravato® is not approved for use in pediatric patients.

VII. Dosing and Administration

The usual dosing regimens for the antidepressants are listed in Table 13.

Table 13. Usual Dosing Regimens for the Antidepressants[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Monoamine Oxidase Inhibitors			
Isocarboxazid	Depression: Tablet: 10 mg twice per day; maximum, 60 mg/day; reduce dose to 10 to 20 mg/day when condition improves	Safety and efficacy in children have not been established.	Tablet: 10 mg
Phenelzine	Depression: Tablet: 15 mg three times per day; may increase to 60 to 90 mg/day during the early phase of treatment, then reduce dose for maintenance therapy slowly	Safety and efficacy in children have not been established.	Tablet: 15 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	after maximum benefit is obtained		
Selegiline	Depression: Transdermal patch: initial, 6 mg/24 hours once daily; may titrate based on clinical response in increments of 3 mg/day every two weeks up to a maximum of 12 mg/24 hours	Safety and efficacy in children have not been established.	Transdermal patch: 6 mg/24 hours 9 mg/24 hours 12 mg/24 hours
Tranylcypromine	Depression: Tablet: 10 mg twice daily; increase by 10 mg increments at one- to three-week intervals; maximum, 60 mg/day; usual effective dose, 30 mg/day	Safety and efficacy in children have not been established.	Tablet: 10 mg
Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
Desvenlafaxine	Major depressive disorder: Extended-release tablet: 50 mg once-daily	Safety and efficacy in children have not been established.	Extended-release tablet: 25 mg 50 mg 100 mg
Duloxetine	Chronic musculoskeletal pain: Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once-daily; maximum, 60 mg/day Fibromyalgia: Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once daily; maximum, 60 mg/day Neuropathic pain associated with diabetic peripheral neuropathy: Delayed-release capsule: 60 mg once-daily Generalized anxiety disorder: Delayed-release capsule: initial, 60 mg/day; maintenance, 60 mg once-daily; maximum, 120 mg/day Major depressive disorder: Delayed-release capsule: initial, 40 to 60 mg/day; maintenance (acute treatment), 40 (20 mg twice-daily) to 60 mg/day (once-daily or 30 mg twice-daily); maintenance, 60 mg/day; maximum, 120 mg/day	Generalized anxiety disorder in patients 7 to 17 years of age: Delayed-release capsule: initial, 30 mg/day; maintenance, 30 to 60 mg once daily; maximum, 120 mg/day Fibromyalgia in patients 13 to 17 years of age: Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once daily; maximum, 60 mg/day	Delayed-release capsule: 20 mg 30 mg 40 mg 60 mg
Levomilnacipran	Major depressive disorder: Extended-release capsule: initial, 20 mg once daily for two days, then increase to 40 mg once daily; maintenance, 40 to 120 mg once daily; maximum, 120 mg once daily	Safety and efficacy in children have not been established.	Extended-release capsules: 20 mg 40 mg 80 mg 120 mg Extended-release capsule dose pack: 20 mg (2 capsules),

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			40 mg (26 tablets)
Venlafaxine	Generalized anxiety disorder: Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day Major depressive disorder: Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day Extended-release tablet: initial, 75 mg/day; maintenance, 75 to 225 mg/day; maximum, 225 mg/day Tablet: initial, 37.5 to 75 mg/day administered in two or three divided doses; maintenance, 75 to 225 mg/day; maximum, 375 mg/day Treatment of panic disorder, with or without agoraphobia: Extended-release capsule: initial, 37.5 mg once-daily for one week; maintenance, 75 to 225 mg/day; maximum, 225 mg/day Treatment of social anxiety disorder: Extended-release capsule, extended-release tablet: 75 mg once-daily	Safety and efficacy in children have not been established.	Extended-release capsule: 37.5 mg 75 mg 150 mg Extended-release tablet: 37.5 mg 75 mg 150 mg 225 mg Tablet: 25 mg 37.5 mg 50 mg 75 mg 100 mg
Selective Serotonin-reuptake Inhibitors			
Citalopram	Depression: Capsule, solution, tablet: initial, 20 mg/day; increase dose in 20 mg increments at intervals of no less than one week; maximum dose, 40 mg/day	Safety and efficacy in children have not been established.	Capsule: 30 mg Solution: 10 mg/5 mL Tablet: 10 mg 20 mg 40 mg
Escitalopram	Depression: Solution, tablet: initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week Generalized anxiety disorder: Solution, tablet: Initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week	Depression ≥12 years of age: Solution, tablet: initial, 10 mg/day; dose may be increased to 20 mg/day after at least three weeks General anxiety disorder ≥7 years of age: Solution, tablet: initial, 10 mg/day; dose may be increased to 20 mg/day after at least two weeks	Solution: 5 mg/5 mL Tablet: 5 mg 10 mg 20 mg
Fluoxetine	Bulimia nervosa: Immediate release capsule and tablet, solution: 20 mg once daily; usual dose:	Depression eight to 18 years of age: Immediate release	Delayed release capsule: 90 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	60 mg/day; maximum, 60 mg/day; doses >20 mg may be given once daily or divided twice daily <u>Depression:</u> Immediate release capsule and tablet, solution: 20 mg once daily; usual dose, 20 to 40 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose <u>Obsessive-compulsive disorder:</u> Immediate release capsule and tablet, solution: 20 mg once daily; usual dose: 40 to 80 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose <u>Panic disorder:</u> Immediate release capsule and tablet, solution: initial, 10 mg/day; after one1 week, increase to 20 mg/day; may increase after several weeks; doses >60 mg/day have not been evaluated Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose	capsule and tablet, solution: 10 to 20 mg/day; lower-weight children may be started on 10 mg/day; may increase to 20 mg/day after one week if needed <u>Obsessive-compulsive disorder seven to 18 years of age:</u> Immediate release capsule and tablet, solution: 10 mg/day; in adolescents and higher-weight children, dose may be increased to 20 mg/day after two weeks; range, 10 to 60 mg/day	Immediate release capsule: 10 mg 20 mg 40 mg Immediate release tablet: 10 mg 20 mg 60 mg Solution: 20 mg/5 mL
Fluvoxamine	<u>Obsessive-compulsive disorder:</u> Immediate release tablet: initial, 50 mg at bedtime; adjust dose in 50 mg increments every four to seven days; usual dose, 100 to 300 mg/day; divide total daily dose into two doses; administer larger portion at bedtime; when total daily dose exceeds 100 mg, the dose should be given in two divided	<u>Obsessive-compulsive disorder eight to 17 years of age:</u> Immediate release tablet: initial, 25 mg at bedtime; adjust in 25 mg increments at four- to seven-day intervals; range, 50 to 200 mg/day	Extended release capsule: 100 mg 150 mg Immediate release tablet: 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	doses Extended release capsule: initial, 100 mg at bedtime; may be increased in 50 mg increments at intervals of at least one week; usual dose range, 100 to 300 mg/day		100 mg
Paroxetine	Depression: Immediate release tablet, suspension: initial, 20 mg once daily; increase by 10 mg/day increments at intervals of at least one week; maximum dose, 50 mg/day Extended release tablet: initial, 25 mg once daily; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 62.5 mg/day Generalized anxiety disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; doses of 20 to 50 mg/day were used in clinical trials; however, no greater benefit was seen with doses >20 mg Obsessive-compulsive disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range, 20 to 60 mg/day Moderate to severe vasomotor symptoms associated with menopause: Immediate release capsule: 7.5 mg once daily at bedtime Panic disorder: Immediate release tablet, suspension: initial, 10 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range, 10 to 60 mg/day Extended release tablet: initial, 12.5 mg once daily in the morning; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 75 mg/day Premenstrual dysphoric disorder:	Safety and efficacy in children have not been established.	Extended release tablet: 12.5 mg 25 mg 37.5 mg Immediate release capsule: 7.5 mg Suspension: 10 mg/5 mL Immediate release tablet: 10 mg 20 mg 30 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Extended release tablet: initial, 12.5 mg once daily in the morning; dose may be increased to 25 mg/day; dosing changes should occur at intervals of at least one week; may be given daily throughout the menstrual cycle or limited to the luteal phase Posttraumatic stress disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; range, 20 to 50 mg; limited data suggest doses of 40 mg/day were not more efficacious than 20 mg/day Social anxiety disorder: Immediate release tablet, suspension: initial, 20 mg once daily, preferably in the morning; recommended dose, 20 mg/day; range, 20 to 60 mg/day; doses >20 mg/day may not have additional benefit Extended release tablet: initial, 12.5 mg once daily; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 37.5 mg/day		
Sertraline	Depression: Capsule, oral concentrate, tablet: initial, 50 mg/day; may increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime Obsessive-compulsive disorder: Capsule, oral concentrate, tablet: initial, 50 mg/day; may increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime Panic disorder: Oral concentrate, tablet: initial, 25 mg once daily; increased after one week to 50 mg once daily Posttraumatic stress disorder: Oral concentrate, tablet: initial, 25 mg once daily; increased after one week to 50 mg once daily Premenstrual dysphoric disorder: Oral concentrate, tablet: 50 mg daily	Obsessive-compulsive disorder six to 12 years of age: Capsule, oral concentrate, tablet: initial, 25 mg once daily Obsessive-compulsive disorder 13 to 17 years of age: Capsule, oral concentrate, tablet: initial, 50 mg once daily May increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime	Capsule: 150 mg 200 mg Oral concentrate: 20 mg/mL Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	throughout menstrual cycle or limited to the luteal phase of menstrual cycle; patients not responding to 50 mg/day may benefit from dose increases (50 mg increments per menstrual cycle) up to 150 mg/day when dosing throughout menstrual cycle or up to 100 mg/day when dosing during luteal phase only Social anxiety disorder: Oral concentrate, tablet: initial, 25 mg once daily; increased after one week to 50 mg once daily; range, 50 to 200 mg/day		
Serotonin Modulators			
Nefazodone	Depression: Tablet: 200 mg/day divided in two doses initially, with a range of 300 to 600 mg/day in two divided doses thereafter	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg 150 mg 200 mg 250 mg
Trazodone	Major depressive disorder: Tablet: initial, 150 mg/day in three divided doses; maintenance, dose may be increased by 50 mg/day every three to seven days; maximum, 400 (outpatients) and 600 (inpatients) mg/day	Safety and efficacy in children have not been established.	Immediate release tablet: 50 mg 100 mg 150 mg 300 mg
Vilazodone	Major depressive disorder: Tablet: Initial, 10 mg once daily for seven days, then increase to 20 mg once daily for seven days, then may increase to 40 mg daily	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg 40 mg Tablet dose pack: 10 mg (7 tablets), 20 mg (23 tablets)
Vortioxetine	Major depressive disorder: Tablet: initial, 10 mg once daily; maintenance, increase to 20 mg once daily, as tolerated; maximum, 20 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents			
Amitriptyline	Depression: Tablet: 25 to 50 mg/day as a single dose at bedtime or in divided doses; dose may be gradually increased up to 300 mg/day	Depression >12 years of age: Tablet: 10 mg three times per day and 20 mg at bedtime	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg
Amoxapine	Depression: Tablet: initial, 25 mg two to three times/day; if tolerated, dosage may be increased to 100 mg two to three times/day; may be given in a single bedtime dose when dosage <300 mg/day; maximum daily dose, 600 mg	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	(inpatients) and 400 mg (outpatients)		
Clomipramine	Obsessive-compulsive disorder: Capsule: initial, 25 mg/day and gradually increase, as tolerated, to 100 mg/day the first two weeks; maximum, 250 mg/day	Obsessive-compulsive disorder >10 years of age: Capsule: initial, 25 mg/day and gradually increase, as tolerated; maximum, 3 mg/kg/day or 200 mg/day, whichever is smaller	Capsule: 25 mg 50 mg 75 mg
Desipramine	Depression: Tablet: initial, 25 to 50 mg/day; increase gradually to 100 to 200 mg/day in divided or single dose; maximum, 300 mg/day	Depression >12 years of age: Tablet: initial, 25 to 50 mg/day; gradually increase to 100 mg/day in single or divided doses; maximum, 150 mg/day	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg
Doxepin	Anxiety: Capsule, oral concentrate: initial, 25 to 75 mg/day at bedtime or in two to three divided doses; may gradually increase up to 300 mg/day; single dose should not exceed 150 mg; select patients may respond to 25 to 50 mg/day Depression: Capsule, oral concentrate: initial, 25 to 75 mg/day at bedtime or in two to three divided doses; may gradually increase up to 300 mg/day; single dose should not exceed 150 mg; select patients may respond to 25 to 50 mg/day Insomnia: Tablet: 3 to 6 mg once daily at bedtime; maximum, 6 mg/day	Safety and efficacy in children have not been established.	Capsule: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg Oral concentrate: 10 mg/mL Tablet: 3 mg 6 mg
Imipramine	Depression: Capsule: initial, 75 mg/day; dosage may be increased to 150 to 200 mg/day; doses >75 mg/day may be administered once daily; in some patients, it may be necessary to employ a divided-dose schedule Tablet: initial, 25 mg three to four times/day; increase dose gradually, total dose may be given at bedtime; maximum, 300 mg/day	Depression (adolescents): Tablet: initial, 30 to 40 mg/day; increase gradually; maximum, 100 mg/day in single or divided doses Pediatric nocturnal enuresis >6 years of age: Tablet: initial, 25 mg one hour before bedtime; if inadequate response after one week of therapy, increase by 25 mg/day; dose should not exceed 2.5 mg/kg/day or 50 mg at bedtime (if 6 to 12	Capsule: 75 mg 100 mg 125 mg 150 mg Tablet: 10 mg 25 mg 50 mg

<table>
<tr><th>Generic Name(s)</th><th>Usual Adult Dose</th><th>Usual Pediatric Dose</th><th>Availability</th></tr>
<tr><td></td><td></td><td>years of age) or 75 mg at bedtime (if ≥12 years of age)</td><td></td></tr>
<tr><td>Nortriptyline</td><td><u>Depression:</u>
Capsule, solution: 25 mg three to four times daily, up to 150 mg/day</td><td>Safety and efficacy in children have not been established.</td><td>Capsule:
10 mg
25 mg
50 mg
75 mg

Solution:
10 mg/5 mL</td></tr>
<tr><td>Protriptyline</td><td><u>Depression:</u>
Tablet: 15 to 60 mg/day in three to four divided doses</td><td><u>Depression (adolescents):</u>
Tablet: 15 to 20 mg/day in three divided doses</td><td>Tablet:
5 mg
10 mg</td></tr>
<tr><td>Trimipramine</td><td><u>Depression:</u>
Capsule: 50 to 150 mg/day as a single bedtime dose; maximum, 200 mg/day for outpatients and 300 mg/day for inpatients</td><td><u>Depression (adolescents):</u>
Capsule: initial, 50 mg/day, with gradual increments up to 100 mg/day</td><td>Capsule:
25 mg
50 mg
100 mg</td></tr>
<tr><td colspan="4">Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products</td></tr>
<tr><td>Amitriptyline and chlordiazepoxide</td><td><u>Mixed anxiety/depressive disorder:</u>
Tablet: initial, three to four tablets in divided doses; may be increased to six tablets per day as required; some patients respond to smaller doses and can be maintained on two tablets</td><td>Safety and efficacy in children have not been established.</td><td>Tablet:
12.5-5 mg
25-10 mg</td></tr>
<tr><td colspan="4">Antidepressants, Miscellaneous</td></tr>
<tr><td>Brexanolone</td><td><u>Postpartum depression:</u>
Intravenous infusion:

<table><tr><th>Time Interval</th><th>Dose</th></tr><tr><td>0 to 4 hours</td><td>30 µg/kg/hour</td></tr><tr><td>4 to 24 hours</td><td>60 µg/kg/hour</td></tr><tr><td>24 to 52 hours</td><td>90 µg/kg/hour*</td></tr><tr><td>52 to 56 hours</td><td>60 µg/kg/hour</td></tr><tr><td>56 to 60 hours</td><td>30 µg/kg/hour</td></tr></table>*A reduction in dosage to 60 µg/kg/hour may be considered during the 24 to 52-hour time period for patients who do not tolerate 90 µg/kg/hour.</td><td><u>Pediatric postpartum depression >15 years of age:</u>
Intravenous infusion:
Follow adult dosing</td><td>Injection:
100 mg/20 mL single-dose vial</td></tr>
<tr><td>Bupropion</td><td><u>Depression:</u>
Extended release tablet: initial, 150 mg/day in the morning; may increase as early as day four of dosing to 300 mg/day; maximum dose: 450 mg/day

Extended release tablet: initial, 174 mg/day in the morning; may increase as early as day four to 348 mg/day; maximum dose: 522 mg/day

Immediate release tablet: initial, 100 mg twice daily; maximum, 450 mg/day</td><td>Safety and efficacy in children have not been established.</td><td>Extended release tablet:
150 mg (Wellbutrin XL®)
174 mg (Aplenzin®)
300 mg (Wellbutrin XL®)
348 mg (Aplenzin®)
450 mg (Forfivo®)
522 mg (Aplenzin®)</td></tr>
</table>

<table>
<tr><th>Generic Name(s)</th><th>Usual Adult Dose</th><th>Usual Pediatric Dose</th><th>Availability</th></tr>
<tr><td></td><td>Sustained release tablet: initial, 150 mg/day; may increase to 150 mg twice daily by day four if tolerated; target dose, 150 mg twice daily; maximum dose, 400 mg/day

<u>Seasonal affective disorder:</u>
Sustained release tablet: initial, 150 mg/day in the morning; if tolerated, may increase after one week to 300 mg/day

<u>Smoking cessation:</u>
Immediate release tablet: initial, 150 mg once daily for three days; increase to 150 mg twice daily; treatment should continue for seven to twelve weeks</td><td></td><td>Immediate release tablet:
75 mg
100 mg

Sustained release tablet (Wellbutrin SR®):
100 mg
150 mg
200 mg</td></tr>
<tr><td>Dextromethorphan and Bupropion</td><td><u>Depression:</u>
Tablet: Starting dosage is one tablet once daily in the morning. After three days, increase to the maximum recommended dosage of one tablet twice daily, separated by at least eight hours. Do not exceed two doses within the same day.</td><td>Safety and efficacy in children have not been established.</td><td>Tablet:
45-105 mg</td></tr>
<tr><td>Esketamine</td><td><u>Depressive symptoms with major depressive disorder with acute suicidal ideation or behavior (in conjunction with an oral antidepressant)</u>:
Nasal spray: Weeks one to four;
84 mg twice per week; may reduce to 56 mg twice per week based on tolerability. Evaluate the need for continued treatment beyond four weeks; treatment beyond 4 weeks with an oral antidepressant has not been evaluated.

<u>Treatment-resistant depression (in conjunction with an oral antidepressant):</u>
Nasal spray:
<table><tr><td colspan="3">Induction Phase</td></tr><tr><td>Weeks one to four</td><td>Administer twice per week</td><td>First dose: 56 mg

Subsequent doses: 56 mg or 84 mg</td></tr><tr><td colspan="3">Maintenance Phase</td></tr><tr><td>Weeks five to eight</td><td>Administer once per week</td><td>56 mg or 84 mg</td></tr><tr><td>Weeks nine</td><td>Administer every two</td><td>56 mg or 84 mg</td></tr></table></td><td>Safety and efficacy in children have not been established.</td><td>Nasal spray:
28 mg
56 mg kit (28 mg x 2)
84 mg kit (28 mg x 3)</td></tr>
</table>

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	and after | weeks or once per week* | *Dosing frequency should be individualized to the least frequent dosing to maintain remission/response. Must be administered under the direct supervision of a healthcare provider.		
Mirtazapine	Depression: Orally disintegrating tablet, tablet: initial, 15 mg at bedtime; titrate up to 15 to 45 mg/day with dose increases made no more frequently than every one to two weeks	Safety and efficacy in children have not been established.	Orally disintegrating tablet: 15 mg 30 mg 45 mg Tablet: 7.5 mg 15 mg 30 mg 45 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antidepressants are summarized in Table 14.

Table 14. Comparative Clinical Trials with the Antidepressants

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td colspan="5">Depression</td></tr>
<tr><td>Meltzer-Brody et al.[23]
(2018)
HUMMINGBIRD study (202B)

Brexanolone 60 µg/kg/hour infusion

vs

brexanolone 90 µg/kg/hour infusion

vs

placebo</td><td>DB, MC, PC, RCT

Patients aged 18 to 45 years old that are ≤6 months postpartum with moderate PPD defined as a HAM-D score ≥26 (study 1) or 20 to 25 (study 2) with onset of an MDE no earlier than the third trimester or within four weeks postpartum</td><td>N=138

30 days</td><td>Primary:
Change from baseline in mean Hamilton Depression Rating Scale (HAM-D) total score at the end of the 60-hour infusion

Secondary:
Change from baseline in HAM-D total score at all time points throughout the study period, proportion of achieving HAM-D response, proportion of patients achieving HAM-D remission, response in Clinical Global Impression-Improvement (CGI-I), change from baseline in Montgomery-Asberg Depression</td><td>Primary:
At the end of the 60-hour infusion, the LS mean reduction in HAM-D total score was 19.5 points in the brexanolone 60 µg/kg/hour group (BRX60) and 17.7 points in the brexanolone 90 µg/kg/hour group (BRX90) compared to 14.0 points in the placebo group, with a mean difference compared to placebo of -5.5 for the BRX60 group (95% CI, -8.8 to -2.2; P=0.0013) and -3.7 for the BRX90 group (95% CI, -6.9 to -0.5; P=0.0252) respectively.

Secondary:
The change from baseline in HAM-D total scores at all time points throughout the study period are outlined below.

LS mean change in HAM-D scores from baseline
<table>
<tr><th rowspan="2">Time from infusion initiation</th><th colspan="3">LS mean change from baseline (SE)</th></tr>
<tr><th>BRX60</th><th>BRX90</th><th>Placebo</th></tr>
<tr><td>2 hours</td><td>-5.0 (0.7)</td><td>-4.9 (0.7)</td><td>-5.0 (0.7)</td></tr>
<tr><td>4 hours</td><td>-9.0 (0.9)</td><td>-7.2 (0.9)</td><td>-6.9 (0.8)</td></tr>
<tr><td>8 hours</td><td>-10.2 (1.0)</td><td>-8.5 (1.0)</td><td>-8.1 (0.9)</td></tr>
<tr><td>12 hours</td><td>-11.0 (1.1)</td><td>-9.1 (1.0)</td><td>-9.8 (1.0)</td></tr>
<tr><td>24 hours</td><td>-15.0 (1.2)</td><td>-13.0 (1.2)</td><td>-10.7 (1.1)</td></tr>
<tr><td>36 hours</td><td>-17.7 (1.2)</td><td>-13.9 (1.2)</td><td>-12.6 (1.1)</td></tr>
<tr><td>48 hours</td><td>-18.0 (1.3)</td><td>-16.9 (1.2)</td><td>-13.6 (1.2)</td></tr>
<tr><td>72 hours</td><td>-19.7 (1.3)</td><td>-17.2 (1.2)</td><td>-14.7 (1.2)</td></tr>
<tr><td>7 days</td><td>-17.4 (1.4)</td><td>-14.9 (1.3)</td><td>-13.3 (1.3)</td></tr>
<tr><td>30 days</td><td>-19.5 (1.4)</td><td>-17.6 (1.4)</td><td>-13.8 (1.3)</td></tr>
</table>
The percentage of patients achieving HAM-D response defined as a ≥50% reduction from baseline in HAM-D total score was 86.5% for BRX60, 74.4% for BRX90, and 55.8% for placebo at hour 60 (P=0.0052 and</td></tr>
</table>

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td>Rating Scale (MADRS) total score</td><td>P=0.0493, respectively) and 82.9% for BRX60, 69.4% for BRX90, and 50.0% for placebo at day 30 (P=0.0052 for BRX60).

The percentage of patients achieving HAM-D remission (defined as a total score ≤7) for BRX60, BRX90, and placebo was 51.4%, 30.8%, and 16.3%, respectively at hour 60 (P=0.0013 for BRX60) and 48.6%, 38.9% and 31.0%, respectively at day 30 (P values not reported).

The LS mean difference in CGI-I score as compared to placebo was -0.83 for BRX60 and -0.67 for BRX90 at hour 60 (P=0.0003 and P=0.0029, respectively) and -0.80 for BRX60 and -0.53 for BRX90 at day 30 (P=0.0019 and P=0.0341, respectively).

The proportion of patients who achieved a CGI-I response at 60 hours after the infusion was 83.8% (31/37) in the BRX60 group and 82.1% (32/39) in the BRX90 group compared to 55.8% (24/43) in the placebo group (OR, 4.0; 95% CI, 1.3 to 11.7; P=0.0131 and OR, 4.0; 95% CI, 1.4 to 11.6; P=0.0095, respectively).

The change from baseline in MADRS total score was -6.9 for BRX60 and -4.2 for BRX90 at hour 60 versus placebo (P=0.0054 and P=NS, respectively).</td></tr>
<tr><td>Meltzer-Brody et al.[23]
(2018)
HUMMINGBIRD study (202C)

Brexanolone 90 µg/kg/hour infusion

vs

placebo</td><td>DB, MC, PC, RCT

Patients aged 18 to 45 years old that are ≤6 months postpartum with moderate PPD defined as a HAM-D score between 20 and 25 with onset of an MDE during the third trimester or within four weeks postpartum</td><td>N=108

30 days</td><td>Primary:
Change from baseline in mean HAM-D total score at the end of the 60-hour infusion

Secondary:
Change from baseline in HAM-D total score at all time points throughout the study period, proportion of</td><td>Primary:
At the end of the 60-hour infusion, the LS mean reduction in HAM-D total score was 14.6 points in the brexanolone 90 µg/kg/hour group (BRX90) compared to 12.1 points in the placebo group (P=0.0160).

Secondary:
The change from baseline in HAM-D total scores at all time points throughout the study period are outlined below.

LS mean change in HAM-D scores from baseline
<table>
<tr><th rowspan="2">Time from infusion initiation</th><th colspan="2">LS mean change from baseline (SE)</th></tr>
<tr><th>BRX90</th><th>Placebo</th></tr>
<tr><td>2 hours</td><td>-4.6 (0.6)</td><td>-4.0 (0.6)</td></tr>
<tr><td>4 hours</td><td>-7.3 (0.7)</td><td>-6.6 (0.7)</td></tr>
<tr><td>8 hours</td><td>-8.4 (0.7)</td><td>-7.4 (0.7)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td>patients achieving HAM-D response, proportion of patients achieving HAM-D remission, response in CGI-I, change from baseline in MADRS total score</td><td>
<table>
<tr><td>12 hours</td><td>-9.1 (0.8)</td><td>-8.0 (0.8)</td></tr>
<tr><td>24 hours</td><td>-11.4 (0.8)</td><td>-9.8 (0.8)</td></tr>
<tr><td>36 hours</td><td>-12.3 (0.8)</td><td>-10.5 (0.8)</td></tr>
<tr><td>48 hours</td><td>-13.0 (0.9)</td><td>-10.6 (0.9)</td></tr>
<tr><td>72 hours</td><td>-15.3 (0.8)</td><td>-11.8 (0.8)</td></tr>
<tr><td>7 days</td><td>-14.0 (1.1)</td><td>-10.7 (1.0)</td></tr>
<tr><td>30 days</td><td>-14.7 (1.0)</td><td>-15.2 (0.9)</td></tr>
</table>

The percentage of patients achieving HAM-D response defined as a ≥50% reduction from baseline in HAM-D total score was 67.3% for BRX90 and 49.1% for placebo at hour 48 (P=0.0146) and 66.0% for BRX90 and 50.9% for placebo at day 7 (P=0.0482).

The percentage of patients achieving HAM-D remission (defined as a total score ≤7) for BRX90 and placebo was 42.9% vs 24.5% at hour 48 (P=0.0158) and 56.0% vs 32.1% at day seven (P=0.0046).

The proportion of patients who achieved a CGI-I response at 60 hours after the infusion was 79.6% (39/49) in the BRX90 group compared to 55.8% (29/52) in the placebo group (OR, 5.0; 95% CI, 2.0 to 12.5; P=0.005). The LS mean difference in CGI-I score for BRX90 as compared to placebo was -0.51 at hour 24 (P=0.0047) and -0.53 at day seven (P=0.0266).

The change from baseline in MADRS total score was -4.9 at hour 60 versus placebo (P=0.0.0033).</td></tr>
<tr><td>Koshino et al.[24] (2013)

Bupropion SR 150 mg daily

vs

bupropion SR 150 mg BID</td><td>DB, MC, PC, RCT

Patients 18 to 64 years of age with MDD in Japan or South Korea</td><td>N=569

8 weeks</td><td>Primary:
Mean change from baseline in MADRS total score at week eight

Secondary:
Comparison of change from baseline for each group in MADRS</td><td>Primary:
The mean change from baseline in MADRS total scores was decreased for bupropion SR 150 mg daily, bupropion 150 mg BID and placebo; however no significant difference from placebo (-14.4; P=0.853, -12.9; P value not reported, -13.9; P value not reported, respectively).

Secondary:
Both MADRS and IDS-SR total scores consistently decreased (weeks one, two, four, six and eight) throughout the study for all groups, including placebo; however, neither bupropion treatment group significantly differed from placebo in either MADRS or IDS-SR in total scores. When MADRS</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			total scores and IDS-SR total scores at weeks one, two, four, six and eight; MADRS total scores stratified by location at week eight for each group	results were stratified by location (Japan or South Korea), no significant differences were observed in change from baseline in MADRS total score at week eight.
Clayton et al.[25] (2006) Bupropion ER 300 to 450 mg daily vs escitalopram 10 to 20 mg daily vs placebo	DB, PC, RCT Adult outpatients with moderate-to-severe MDD with normal sexual function	N=830 8 weeks	Primary: Orgasm dysfunction at eight weeks and incidence of worsened sexual functioning; CSFQ, HAM-D_{17} Secondary: Not reported	Primary: The incidence of worsened sexual functioning at the end of the treatment period was statically significantly lower with bupropion ER than with escitalopram (P<0.05), not statistically different between bupropion ER and placebo (P>0.067), and statistically significantly higher with escitalopram than with placebo (P<0.001). The percentages of patient with orgasm dysfunction at week eight were 15% with bupropion ER, 30% with escitalopram, and 15% with placebo. The mean change in CSFQ sores for all domains at week eight was statistically significantly worse for escitalopram compared to bupropion ER (P<0.05). Bupropion did not statistically differ from escitalopram with respect to mean change in HAM-D_{17} total score, response or remission rates. Secondary: Not reported
Hewett et al.[26] (2009) Bupropion ER 150 mg/day for 4 weeks, then 300 mg/day	DB, MC, PC, RCT Patients 18 to 64 years of age with MDD	N=576 8 weeks	Primary: Mean change from baseline at week eight in the MADRS total score (LOCF) Secondary:	Primary: The mean changes from baseline at week eight (LOCF) in MADRS total score were greater for patients receiving bupropion ER and venlafaxine ER compared to patients receiving placebo: -16.0 for bupropion ER (P=0.006 vs placebo), -17.1 for venlafaxine ER (P<0.001 vs placebo) and -13.5 for placebo. There was no significant difference between the bupropion ER group and the venlafaxine ER group (95% CI, -0.7 to 2.9).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs venlafaxine ER 75 mg/day for 4 weeks, then 150 mg/day vs placebo			MADRS total score (observed cases), MADRS subscore, percentage of MADRS responders and remitters at week eight; CGI-I score at week eight; CGI-S score and HAMA total score at weeks one, two, four, six and eight	Secondary: The mean changes from baseline to week eight (observed cases) in MADRS total scores were significantly greater for bupropion ER and venlafaxine ER patients compared to the placebo group: -18.2 for bupropion ER (P=0.003), -18.5 for venlafaxine ER (P<0.001) and -15.8 for placebo. Significant improvements from baseline in MADRS sadness and concentration difficulties scores were observed for bupropion ER (-2.2; P<0.001 and -1.8; P=0.004, respectively) and venlafaxine ER (-2.3; P<0.001 and -1.9; P<0.001, respectively) compared to placebo at week eight (-1.7 and -1.4, respectively). Significant improvements in MADRS lassitude score were found for venlafaxine ER compared to placebo (-1.8 vs -1.5; P=0.009), but not for bupropion ER (-1.7 vs -1.5; P=0.140). A larger proportion of patients in the bupropion ER and venlafaxine ER groups were classified as MADRS responders (≥50% reduction in MADRS total score) and remitters (MADRS total score ≤11) at week eight compared to the placebo group. Response rates were 57% for bupropion ER (P=0.033), 65% for venlafaxine ER (P<0.001), and 46% for placebo. Remission rates were 47% for bupropion ER (P=0.004), 51% for venlafaxine ER (P<0.001), and 32% for placebo. CGI-I response rates for both active treatment groups were significantly better than placebo with 68% of bupropion ER patients (P<0.001) and 65% of venlafaxine ER patients (P=0.009) rated ‘much improved’ or ‘very much improved’ at week eight compared to 53% of placebo patients. Significantly greater mean decreases from baseline in SDS total scores were observed for bupropion ER (-8.4; P=0.003) and venlafaxine ER (-9.0; P<0.001) compared to placebo (-6.2). The mean change from baseline in patient satisfaction with study medication was significantly greater for bupropion ER (4.9; P=0.005) and venlafaxine ER (5.2; P<0.001) than placebo (4.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Weihs et al.[27] (2000) Bupropion SR 100 to 300 mg/day vs paroxetine 10 to 40 mg/day	DB, MC, RCT Patients ≥60 years of age with MDD	N=100 6 weeks	Primary: HAM-D, HAMA, CGI-I, CGI-S scores Secondary: Adverse effects	Primary: Measurements of efficacy were similar between the treatment groups, with both showing improved scores on all depression rating scales. Secondary: Somnolence and diarrhea were more common in paroxetine-treated patients (P<0.05). Headache, insomnia, dry mouth, agitation, dizziness, and nausea occurred in >10% of patients in both groups.
Kavoussi et al.[28] (1997) Bupropion SR 100 to 300 mg/day vs sertraline 50 to 200 mg/day	DB, PG, RCT Outpatients with moderate-to-severe MDD	N=248 16 weeks	Primary: HAM-D, HAMA, CGI-I, CGI-S Secondary: Adverse effects	Primary: Mean HAM-D, HAMA, CGI-I, and CGI-S scores improved over the course of treatment in both the bupropion SR group and the sertraline group; no between-group differences were observed on any of the scales. Secondary: Orgasm dysfunction was significantly (P<0.001) more common in sertraline-treated patients compared to bupropion SR-treated patients. Adverse events (nausea, diarrhea, somnolence, and sweating) were experienced more frequently (P<0.05) in sertraline-treated patients. No differences were noted between the treatments for vital signs and weight.
Rocca et al.[29] (2005) Citalopram 20 mg/day vs sertraline 50 mg/day	DB, RCT Patients >65 years of age with minor depressive disorder or subsyndromal depressive symptomatology	N=138 8 weeks	Primary: Change in depressive symptoms and remission rates (HAM-D) Secondary; Not reported	Primary: Both treatments induced notable improvement of depressive symptoms. No statistically significant differences were found between the two treatments in decreases from baseline HAM-D scores. At the end of the trial, the mean total HAM-D score had fallen 55.0% in the citalopram group and 52.7% in the sertraline group. No significant differences in remission rates were observed between the two agents. For one month, three month, and end follow-up periods, P=0.3466, 0.7570, and 0.2537, respectively. Secondary; Not reported
Clayton et al.[30]	DB	N=422	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2013) Desvenlafaxine 50 mg/day vs placebo	Adult outpatients with MDD	12 weeks	Mean change from baseline Arizona Sexual Experiences Scale scores Secondary: Not reported	Among women (desvenlafaxine, n=184; placebo, n=92), baseline scores were 20.0 (5.2) and 20.5 (5.3) for desvenlafaxine and placebo, respectively; mean changes at week 12 were -1.93 (0.37) and -1.03 (0.54), respectively (mean difference: 0.90 [-0.38 to 2.18]; P=0.169). Among men (desvenlafaxine, n=97; placebo, n=49), baseline scores were 16.4 (4.9) and 15.9 (4.8) for desvenlafaxine and placebo, respectively; mean changes at week 12 were -1.13 (0.47) and -1.06 (0.70), respectively (mean difference: 0.07 [-1.59 to 1.74]; P=0.932). Significantly greater orgasmic dysfunction at week 12 was observed in the subgroup of men without baseline sexual dysfunction treated with desvenlafaxine relative to placebo. Conversely, women without baseline sexual dysfunction experienced poorer overall sexual functioning and orgasm satisfaction at week 12 with placebo relative to desvenlafaxine treatment. Subgroup analyses of treatment responders and nonresponders found no difference in the proportion of men or women that developed or had resolution of sexual dysfunction in the desvenlafaxine and placebo groups.
Rosenthal et al.[31] (2013) Desvenlafaxine 50 mg/day vs placebo	DB, MC, PC, RCT Adult outpatients age >18 years of age with MDD (DSM-IV criteria) and a HDRS17 total score >20 at screening and baseline	N=874 11 months	Primary: Time to relapse (HDRS17 total score >16, discontinuation for unsatisfactory response, hospitalization for depression, suicide attempt, or suicide) Secondary: Safety and tolerability	Primary: Time to relapse was significantly shorter for placebo vs desvenlafaxine (P<0.001). At the end of the six-month DB treatment, the estimated probability of relapse was 30.2% for placebo vs 14.3% for desvenlafaxine 50 mg/day. Secondary: Safety and tolerability results were generally consistent with those in short-term studies of desvenlafaxine 50 mg/day.
Dunlop et al.[32] (2011)	DB, PC, RCT Gainfully employed	N=427 12 weeks	Primary: HAM-D-17 total score	Primary: Desvenlafaxine demonstrated superiority over placebo beginning at week two, which continued through week 12. Adjusted mean endpoint scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Desvenlafaxine 50 mg/day vs placebo	(≥20 hours/week) outpatients with MDD		Secondary: SDS, safety	with desvenlafaxine and placebo were 9.33 and 11.45, respectively. Mean change scores were -12.61±0.45 and -10.50±0.60 with desvenlafaxine and placebo, respectively. The adjusted mean difference in change from baseline between desvenlafaxine and placebo at week 12 was 2.12 (95% CI, 0.78 to 3.46; P=0.002). Secondary: The adjusted mean difference in change from baseline score on the SDS between the desvenlafaxine and placebo at week 12 was 1.33 (95% CI, -0.09 to 2.76), which narrowly missed significance (P=0.067). There were six serious adverse events (no deaths) that occurred in four and two desvenlafaxine- and placebo-treated patients. None of these events were considered non-treatment related. No new safety concerns about desvenlafaxine were identified from safety analyses.
Kornstein et al.[33] (2010) Desvenlafaxine 100 or 200 mg/day vs placebo	DB, MC, PC, RCT Perimenopausal and post-menopausal women 40 to 70 years of age with MDD, single or recurrent episode	N=387 8 weeks	Primary: HAM-D-17 total score Secondary: CGI-I, CGI-S, MADRS, HAMA, QIDS-SR, MRS, EQ-5D, VAS-PI, safety	Primary: Baseline reductions in HAM-D-17 total scores were significantly greater with desvenlafaxine (adjusted mean change, -12.64) compared to placebo (-8.33; P<0.01). Significant differences between treatments were observed at week one (P=0.044) and were sustained though week eight (week two; P=0.013, weeks three to eight; P<0.001). Both perimenopausal (adjusted mean change, -10.96; P=0.003) and postmenopausal (-11.09; P<0.001) subgroups achieved significant reductions in HAM-D-17 total scores with desvenlafaxine compared to placebo. The treatment effect (adjusted mean difference from placebo) in these two populations were -4.07 (95% CI, -6.77 to -1.37) and -2.37 (95% CI, -5.07 to -1.47). HAM-D-17 based response (58.6%) and remission (38.2%) rates were significantly higher with desvenlafaxine compared to placebo (31.6 and 22.4%; P<0.001 and P=0.008, respectively). Secondary: Desvenlafaxine achieved significant improvement compared to placebo on all secondary outcomes. Desvenlafaxine-treated patients had significantly lower CGI-I scores at week eight compared to placebo-treated patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(2.00 vs 2.82; P<0.001); a significantly higher percentage of patients receiving desvenlafaxine had scored 1 (very much improved) or 2 (much improved) compared to patients receiving placebo (67.7 vs 41.2%; P<0.001). In total, 7.4 and 3.2% of desvenlafaxine- and placebo-treated patients discontinued study medication due to an adverse event. The event cited most commonly by patients discontinuing due to an adverse event was hypertension (five vs zero patients). Treatment-emergent adverse events were reported by 85.2 and 75.2% of desvenlafaxine- and placebo-treated patients. Most events were mild or moderate in severity. The most common treatment-emergent adverse events were dry mouth (24 vs 10%), somnolence (15 vs 7%), constipation (14 vs 6%), hypertension (7 vs 2%), sweating (7 vs 2%), dyspepsia (6 vs 2%), and anorexia (6 vs <1%). Serious adverse events were reported by three patients receiving desvenlafaxine (chest pain and hypertension, medication error and psychotic depression, and infection) and two patients receiving placebo (cerebrovascular disorder and skin carcinoma). No deaths were reported during the study or within 30 days after its conclusion.
Rickels et al.[34] (2010) Desvenlafaxine 200 to 400 mg/day vs placebo After 12 weeks of OL treatment with desvenlafaxine, patients with HAM-D-17 total score ≤11 were randomized to	DB, PC, RCT Patients 18 to 75 years of age with MDD, single or recurrent episode, without psychotic features	N=374 (DB phase) N=575 (OL phase) 12 weeks of OL treatment, followed by a 6-month, DB phase	Primary: Time until relapse (HAMD-D-17 total score ≥16 at any visit, CGI-I score ≥6 at any visit, or discontinuation due to unsatisfactory response) Secondary: HAM-D-17 total score, CGI-I, CGI-S, HAM-D-6, Covi Anxiety score, safety	Primary: Patients receiving desvenlafaxine experienced significantly longer times to relapse of MDD compared to patients receiving placebo during DB treatment (P<0.0001). The proportions of patients relapsing were 42 and 24% of patients receiving placebo and desvenlafaxine, respectively (P<0.001). Secondary: A significant difference in HAM-D-17 total scores in favor of desvenlafaxine was observed from DB week three onward (P<0.001). At the final evaluation, adjusted mean changes were 0.85 and 5.03 for desvenlafaxine and placebo, respectively. Desvenlafaxine was also associated with significant differences compared to placebo on CGI-I, CGI-S, HAM-D-6, and Covi Anxiety scores. The most common primary reason cited for discontinuation of treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
continue desvenlafaxine or be switched to placebo.				during the OL phase was adverse events (19%), which consisted of nausea, dizziness, and insomnia. A total of 101 (55%) and 58 (31%) patients receiving placebo and desvenlafaxine discontinued treatment during the DB phase. The most frequent adverse event reported as the reason for discontinuation during the DB phase was depression (14 patients receiving placebo vs seven patients receiving desvenlafaxine). During the OL phase the most commonly reported adverse events with desvenlafaxine were nausea (42%), dry mouth (32%), headache (26%), dizziness (23%), hyperhidrosis (21%), insomnia (20%), constipation (15%), decreased appetite (12%), fatigue (12%), somnolence (11%), diarrhea (10%), tremor (10%), vomiting (8%), sedation (5%), and blurred vision (5%). During the DB phase, treatment-emergent adverse events were reported by 73 and 82% of patients receiving desvenlafaxine and placebo, respectively. The most commonly reported events with desvenlafaxine were headache (24%), dizziness (15%), nausea (14%), fatigue (13%), hyperhidrosis (13%), diarrhea (9%), abnormal dreams (9%), depression (8%), insomnia (8%), influenza (7%), irritability (7%) , back pain (6%), upper respiratory tract infection (6%), abdominal pain (5%), anxiety (5%), muscle spasms (5%), nasopharyngitis (5%), tremor (5%), delayed ejaculation (5% in men), erectile dysfunction (5% in men), vomiting (4%), vertigo (3%), myalgia (2%), paresthesia (2%), and altered mood (1%).
Clayton et al.[35] (abstract) (2009) Desvenlafaxine 50 to 400 mg/day vs placebo	DB, PC, RCTs (integrated analysis of short-term 9 trials) Adult outpatients with MDD	N=2,950 8 weeks	Primary: Treatment-emergent adverse events, laboratory values, vital signs, discontinuation symptoms Secondary: Not reported	Primary: The most common treatment-emergent adverse event was transient nausea that was generally mild to moderate. The most common sexual dysfunction associated with desvenlafaxine treatment was erectile dysfunction in men (7 vs 1%) and anorgasmia in women (1 vs 0%). One patient receiving desvenlafaxine died of a completed suicide; there were four suicide attempts (three vs one patient[s]) and eight cases of suicidal ideation (five vs three patients) during the on-therapy period. Desvenlafaxine was associated with small but significant mean changes in laboratory assessments, particularly lipid and liver enzyme elevations, and ECGs; few cases of these changes were clinically relevant. Small but significant changes in mean blood pressure occurred with all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				desvenlafaxine doses; clinically meaningful changes were observed in 1 and 2% of placebo- and desvenlafaxine-treated patients. In the overall population, adverse events resulted in discontinuations in 3 and 12% of placebo- and desvenlafaxine-treated patients; in the subset of fixed-dose trials, the rates were 4 and 4 to 18% with placebo and desvenlafaxine. Secondary: Not reported
Feiger et al.[36] (2009) Desvenlafaxine 200 to 400 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD	N=235 8 weeks (plus a 2-week tapering phase)	Primary: HAM-D-17 Secondary: CGI-I, CGI-S, MADRS, HAM-D-6, safety	Primary: No significant difference was observed in the adjusted mean change from baseline in the HAM-D-17 total score between desvenlafaxine and placebo at the final evaluation (difference in adjusted means, 1.6; 95% CI, -0.2 to 3.4). No significant differences were observed between desvenlafaxine and placebo groups for HAM-D-17 clinical response rates at the final evaluation; the logistic regression analysis demonstrated adjusted ORs of 1.456 (95% CI, 0.85 to 2.50; P=0.175) for HAM-D-17 response. No significant difference in HAM-D-17 remission rates was observed between desvenlafaxine and placebo groups at final evaluation; the logistic regression analysis showed an adjusted OR of 1.158 (95% CI, 0.60 to 2.22; P=0.66). Secondary: At final evaluation, significant differences between desvenlafaxine and placebo were observed for the CGI-I (difference in adjusted means: 0.3; 95% CI, 0.0 to 0.6), CGI-S (0.3; 95% CI, 0.0 to 0.6), MADRS (2.9; 95% CI, 0.3 to 5.4), and HAM-D-6 (1.5; 95% CI, 0.5 to 2.6). A significant difference was observed between desvenlafaxine and placebo groups for MADRS clinical response rates; the logistic regression analysis demonstrated an adjusted OR of 1.754 (95% CI, 1.03 to 3.00; P=0.04). Treatment-emergent adverse events were reported by 112 patients (96%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 101 patients (86%) receiving desvenlafaxine and placebo. Treatment-emergent adverse events reported by ≥5% of patients receiving desvenlafaxine and at a frequency at least twice that of the placebo group included nausea, dry mouth, hyperhidrosis, insomnia, somnolence, decreased appetite, tremor, blurred vision, yawning, sedation, vomiting, mydriasis, middle insomnia, initial insomnia, erectile dysfunction, constipation, feeling jittery, and dyspepsia. Nausea, the most frequently reported adverse event in patients receiving desvenlafaxine (36%), was mild to moderate in the majority of cases (88%). Treatment-emergent adverse events resulted in reduction in dose of study medication for six (5%) and two (2%) patients receiving desvenlafaxine and placebo. Taper/post-study-emergent adverse events were consistent with what has been seen in pervious trials of desvenlafaxine and with the SNRIs. Significantly more patients receiving desvenlafaxine (12%) discontinued the study because of treatment-emergent adverse events compared to patients receiving placebo (3%; P=0.008). No deaths or serious adverse events occurred during the study.
Thase et al.[37] (2009) Desvenlafaxine 50 to 400 mg/day vs placebo	MA (9 trials) Outpatients ≥18 years of age with MDD	N=3,023 8 weeks	Primary: HAM-D-17 total score Secondary: MADRS, HAM-D-6, CGI-I, CGI-S, remission and response rates, safety	Primary: Significantly greater improvement with desvenlafaxine vs placebo on HAM-D-17 total scores was observed for the full data set (difference in adjusted means, -1.9; P<0.001). Significance was observed in all fixed-dose (P<0.001 for all) and flexible-dose trials (P=0.24). Secondary: For the overall desvenlafaxine group significant improvement from baseline was observed on all secondary outcome measures at the final evaluation. Overall, desvenlafaxine had a significantly greater change from baseline compared to placebo on the CGI-I, CGI-S, and MADRS total scores from week two onward and in the core symptoms of depression (HAM-D-6 total score) from week one onward. Overall rates of HAM-D-17 response (53 vs 41%) and remission (32 vs 23%) were significantly greater with desvenlafaxine vs placebo (P<0.001 for all). Discontinuation rates due to adverse events increased with desvenlafaxine dose (4 to 18 vs 3%). The most common treatment-emergent adverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				events in the overall data set were nausea, dry mouth, hyperhidrosis, dizziness, and constipation.
Clayton et al.[38] (2015) Desvenlafaxine 50 and 100 mg/day vs placebo	DB, PC, RCT Outpatients ≥18 years of age with MDD, depressive symptoms for ≥30 days before screening and baseline HAM-D-17 total score ≥20; HAM-D-17 item 1 (depressed mood) score ≥2; and CGI-S ≥4	N=909 8 weeks	Primary: HDRS-17 total score Secondary: CGI-I, CGI-S, ASEX	Primary: A statistically significantly greater change from baseline in HDRS-17 total score was observed for both desvenlafaxine groups compared with placebo after adjusting for multiplicity (desvenlafaxine 50 mg, P=0.006; desvenlafaxine 100 mg, P<0.001). Secondary: Statistically significant improvement from baseline in CGI-S scores was observed at week eight for both desvenlafaxine dose groups compared with placebo. The adjusted mean difference versus placebo was 0.20 (95% CI, 0.05 to 0.34; P=0.009) for the desvenlafaxine 50-mg group and 0.28 (95% CI, 0.13 to 0.43; P<0.001) for the desvenlafaxine 100-mg group. Pairwise comparisons of CGI-I scores for each desvenlafaxine group versus placebo were statistically significant (desvenlafaxine 50 mg, P=0.029; desvenlafaxine 100 mg, P<0.001, without adjustment for multiplicity). At week eight (LOCF), ASEX total and individual item scores were comparable for both 50 and 100 mg doses of desvenlafaxine and placebo, with widely overlapping confidence intervals.
Boyer et al.[39] (2008) Desvenlafaxine 50 and 100 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD, depressive symptoms for ≥30 days before screening and baseline HAM-D-17 total score ≥20; HAM-D-17 item 1 (depressed mood) score ≥2; and CGI-S ≥4	N=438 8 weeks (plus a 1-week taper phase)	Primary: HAM-D-17 total score Secondary: CGI-I, MADRS, CGI-S, VAS-PI, Covi Anxiety Scale total scores, remission rates, responder rates, safety	Primary: In a LOCF analysis, adjusted mean baseline changes in HAM-D-17 total scores were significantly greater with desvenlafaxine 50 (-13.2; P=0.002) and 100 mg/day (-13.7; P<0.001) compared to placebo (-10.7). Secondary: Significant differences on CGI-I scores were observed with desvenlafaxine 50 (P=0.002) and 100 mg/day (P<0.001) compared to placebo. For MADRS total score, the between-group difference vs placebo in adjusted mean was 3.1 (95% CI, 1.0 to 5.2) with desvenlafaxine 50 mg/day and 4.2 (95% CI, 2.1 to 6.3) with desvenlafaxine 100 mg/day. Adjusted mean changes from baseline were significantly greater with desvenlafaxine compared to placebo starting at week four (P=0.036 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.004, respectively), and were sustained until the final evaluation (P=0.004 and P<0.001, respectively). For CGI-S score at final evaluation, adjusted mean changes from baseline were significantly greater than placebo for desvenlafaxine 50 (P=0.003) and 100 mg/day (P<0.001). Significant separation from placebo was observed beginning at week six and four for desvenlafaxine 50 (P=0.002) and 100 mg/day (P=0.027), and both groups remained significantly different through the final evaluation. Results of the VAS-PI are not reported because of the heterogeneity of the format of the translated scale; it was impossible to properly analyze the corresponding data. For Covi Anxiety Scale total score at final evaluation, adjusted mean changes from baseline were significantly greater than placebo for desvenlafaxine 50 (P=0.001) and 100 mg/day (P=0.004). The adjusted OR for response relative to placebo was 1.943 (95% CI, 1.24 to 3.05) and 1.798 (95% CI, 1.14 to 2.83) with desvenlafaxine 50 and 100 mg/day (P=0.004 and P=0.011). For remission rates, the adjusted OR for remission relative to placebo was 1.488 (95% CI, 0.93 to 2.38) and 2.117 (95% CI, 1.32 to 3.39) with desvenlafaxine 50 and 100 mg/day (P=0.099 and P=0.002). Responder rates were significantly higher with desvenlafaxine 50 (65%) and 100 mg/day (63%) compared to placebo (50%; P=0.005 and P=0.018, respectively; NNT, 6.5 and 7.4). Significantly more patients receiving desvenlafaxine 100 mg/day achieved remission compared to patients receiving placebo (45 vs 29%, respectively; P=0.003; NNT, 6.1). Most of the treatment-emergent adverse events were mild or moderate in severity. The most common treatment-emergent adverse events were nausea, dizziness, insomnia, constipation, fatigue, anxiety, and decreased appetite.
Liebowitz et al.[40] (abstract) (2008)	DB, MC, PC, PG, RCT	N=447 8 weeks	Primary: Change from baseline to final	Primary: There was a significant decrease in the HAM-D-17 score from baseline in the desvenlafaxine 50 mg group (-11.5; P=0.018) but not for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Desvenlafaxine 50 or 100 mg/day vs placebo	Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, and CGI-S score ≥4	(plus a 1-week taper)	on-therapy evaluation on HAM-D-17score Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease of ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17score decrease to ≤7%), SDS, WHO-5, safety	desvenlafaxine 100 mg group (-11; P=0.065) compared to the placebo group (-9.53). Secondary: The decrease from baseline in the CGI-I score was not considered significant for the desvenlafaxine 50 mg group (P=0.085) and the 100 mg group (P=0.076) compared to the placebo group. The decrease from baseline in CGI-S scores were not significantly different than the desvenlafaxine 50 mg (P=0.074) and 100 mg groups (P=0.208) compared to the placebo group. There was a significant decrease from baseline in MADRS scores in the desvenlafaxine 50 mg group (P=0.022) but not the 100 mg group (P=0.095). VAS-PI overall pain score showed significant improvement compared to baseline in the 100 mg group (P=0.041) but not for the 50 mg group (P=0.223). There was no significant difference between the desvenlafaxine 50 and 100 mg groups compared to the placebo group in terms of HAM-D-17 rates of response (P=0.133, P=0.246, respectively) and remission (P=0.075, P=0.194, respectively). The desvenlafaxine 50 mg group showed significant improvements from baseline in SDS score (-8.96; P=0.012) and WHO-5 score (6.68; P=0.020) compared to the placebo group. There were no significant differences from baseline in the 100 mg group compared to the placebo group in SDS or WHO-5 score. The most common adverse events seen (incidence ≥10% and at twice the rate in the placebo group) with desvenlafaxine treatment included: dry mouth, constipation, insomnia, decreased appetite, hyperhidrosis and dizziness (P values not reported).
Liebowitz et al.[41] (2007)	DB, MC, PC, PG, RCT	N=247 8 weeks	Primary: Change from baseline to final	Primary: There was no significant difference in the reduction of HAM-D-17 score from baseline between the desvenlafaxine and placebo group (14.1 vs 15.1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Desvenlafaxine 100 mg/day for days 1 to 14, increasing to 200 mg/day vs placebo	Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, a HAM-D item 1 (depressed mood) score ≥2 and CGI-S score ≥4		on-therapy evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, MADRS, CGI-S, VAS-PI, vital signs, safety	respectively; P=0.277). Secondary: There was no significant difference between CGI-I scores between the desvenlafaxine and the placebo group compared to baseline (2.5 vs 2.7 respectively; P value not reported). The CGI-S showed no difference from baseline between the desvenlafaxine and placebo groups (3.1 vs 3.3 respectively; P value not reported). Improvement was demonstrated at final evaluation between desvenlafaxine and placebo on the MADRS scale (16.8 vs 19.5 respectively; P=0.047), the VAS-PI overall pain scale (15.6 vs 11.6 respectively; P=0.008), the VAS-PI back pain scale (13.1 vs 20.5 respectively; P=0.006) and the VAS-PI arm, leg or joint pain scale (13.3 vs 21.6 respectively; P<0.001). There was a significant increase from baseline in supine SBP (3.76 vs -1.59; P<0.001, respectively) and supine DBP (1.85 vs -0.91; P=0.003 respectively) in the desvenlafaxine group compared to the placebo group. There was a significant decrease in body weight seen in the desvenlafaxine group compared to the placebo group (-0.74 vs 0.36 kg; P<0.001). There was an increase in heart rate from baseline observed in the desvenlafaxine group (4.27 beats per minute; P<0.01) and a decrease from baseline in the placebo group (-2.27 beats per minute; P<0.01). A decrease in the QT interval was observed in the desvenlafaxine group from baseline (-4.27 ms; P value not significant) and an increase in QT interval from baseline was observed in the placebo group (4.90; P<0.05). The difference in these values was considered to be statistically significant (P=0.01). Anorexia (P<0.001), constipation (P<0.05), dry mouth (P<0.01), nausea (P<0.001), tremor (P<0.01) and yawning (P<0.01) were seen more commonly in the desvenlafaxine group compared to the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Demartinis et al.[42] (2007) Desvenlafaxine 100, 200, or 400 mg/day vs placebo	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, a Ham-D item 1 (depressed mood) score ≥2 and CGI-S score ≥4	N=461 8 weeks (plus a 2-week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to ≤7%), SDS, WHO-5, vital signs, safety	Primary: Decrease in HAM-D-17 score from baseline was significantly greater at final on-therapy evaluation in the 100 mg (-10.60; P=0.0038) and 400 mg (-10.75; P=0.0023) groups compared to the placebo group (-7.65). However, the decrease in HAM-D-17 score from baseline in the 200 mg group was not significant (-9.63; P=0.0764) compared to the placebo group. Secondary: There were significant decreases in CGI-I score from baseline for the 100 mg (2.3; P=0.008), 200 mg (2.5; P=0.0462) and 400 mg (2.4; P=0.0129) groups compared to the placebo treated group (2.8). There were significant decreases in CGI-S scores from baseline in the 100 mg (-1.5; 95% CI, 0.2 to 0.8; P=0.002) and 400 mg (-1.5; 95% CI, 0.2 to 0.9; P<0.001) groups compared to the placebo group (-1.0). The CGI-S score difference observed in the 200 mg group was not significant (-1.13; 95% CI, 0.0 to 0.6; P=0.056). The decrease from baseline in MADRS score was significant for the 100 mg group (-13.6; 95% CI, 1.3 to 6.4; P=0.004), the 200 mg group (-13.5; 95% CI, 1.3 to 6.2; P=0.005), and the 400 mg group (-15.2; 95% CI, 3.1 to 8.3; P<0.001) compared to the placebo group (-9.9). Patients in the desvenlafaxine 100 mg group showed a significant improvement from baseline in overall pain score compared to the placebo group on the VAS-PI scale (-13.9 vs 5.9; P=0.002, respectively). There was no significant difference in either the 200 mg (-5.4; P=0.357) or the 400 mg (-10.1; P=0.069) groups. There was a significantly higher OR for response to the 100 mg group (2.15; 95% CI, 1.25 to 3.73; P=0.006) and 400 mg group (1.91; 95% CI, 1.11 to 3.32; P=0.020). The OR for response to the 200 mg group was not significant (1.60; 95% CI, 0.93 to 2.76; P=0.089) compared to the placebo group. There was a significantly higher OR for remission in the 400 mg group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to the placebo group (2.20; 95% CI, 1.17 to 4.14; P=0.014). The OR of the 100 mg group (1.86; 95% CI, 0.99 to 3.52; P=0.053) and 200 mg group (1.73; 95% CI, 0.92 to 3.26; P=0.088) were not significant compared to the placebo group. There was a statistically significant increase in supine pulse rate in the desvenlafaxine 400 mg group compared to baseline (4.19; P<0.001). The increase was considered statistically significant when compared to the placebo group (0.15; P<0.05). The change in supine pulse rate from baseline in the desvenlafaxine 100 mg (-0.03) and 200 mg (1.06) groups were not considered significant compared to the placebo group (P value not significant). The mean increase in supine SBP was considered significant in all groups compared to baseline compared to the placebo group (P<0.05). The increase in DBP was considered significant in all treatment groups compared to baseline (P<0.001 for the 200 and 400 mg groups and P<0.01 for 100 mg group). There was a significant increase in DBP from baseline in both the desvenlafaxine 200 and 400 mg groups compared to the placebo group (P<0.05). The increase in DBP from baseline in the 100 mg group was not considered significant compared to the placebo group (P value not significant). There was a significant decrease in body weight in all desvenlafaxine treatment groups compared to baseline (P<0.001) and to the placebo group (P<0.05). Adverse events that occurred at twice the rate of placebo in at least 5% of desvenlafaxine-treated subjects included: nausea, somnolence, insomnia, dry mouth, sweating, dizziness, nervousness, anorexia, constipation, abnormal ejaculation/orgasm, asthenia and tremor (P values not reported).
Septein-Velez et al.[43] (2007) Desvenlafaxine 200 or 400 mg/day vs	DB, MC, PC, PG, RCT Outpatients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days	N=369 8 weeks (plus a 2-week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary:	Primary: The decrease from baseline in HAM-D-17 score was significantly greater in the 200 mg group (-12.6; P=0.002) and the 400 mg group (-12.1; P=0.008) compared to the placebo group (-9.3). Secondary: A lower CGI-I score was observed in the 200 mg group (P=0.004) and the 400 mg group (P=0.028) compared to the placebo group. There was a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	prior to screening, HAM-D-17 total score ≥20, and CGI-S score ≥4		Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to ≤7%), SDS, WHO-5	significant difference in change in MADRS score from baseline favoring desvenlafaxine in the 200 mg (P=0.001) and 400 mg (P=0.005) groups compared to the placebo group. There was a significant difference in change in CGI-S score from baseline favoring patients treated with desvenlafaxine compared to patient treated with placebo (P=0.001 and P=0.013 for the desvenlafaxine 200 and 400 mg groups, respectively). There was a greater response on the HAM-D-17 rate of response assessment for the 200 mg (60%; P<0.001) and 400 mg (56%; P=0.005) groups compared to the placebo group (38%). A greater degree of remission was observed for the 200 mg group (37%; P=0.017) compared to the placebo group (23%). The degree of remission was not significant for the 400 mg group (P value not reported). The change in VAS-PI overall pain score from baseline favored the desvenlafaxine 200 mg group (P=0.002) compared to the placebo group. The difference between the 400 mg group and the placebo group was not considered significant (P=0.053). There was a significant improvement from baseline in SDS total score for the desvenlafaxine 200 mg (P=0.004) and 400 mg (P=0.004) groups compared to the placebo group. There was a significant improvement from baseline in WHO-5 score for the desvenlafaxine 200 mg (P=0.001) and 400 mg (P=0.005) groups compared to the placebo group.
Tourian et al.[44] (2013) Desvenlafaxine 25 mg/day from days 1 to 14, with subsequent upward titration, to a maximum of 100 mg/day, determined by	MC, OL Japanese patients with MDD who had completed an 8-week, DB, PC study in which patients received 25 or 50 mg/day desvenlafaxine or placebo	N=304 10 weeks	Primary: Safety, HAM-D17 Secondary: Not reported	Primary: Treatment-emergent adverse events were reported by 240 patients (78.9%) during the on-therapy period; the most common adverse events were nasopharyngitis (37.2%), somnolence (11.5%), headache (10.5%), and nausea (10.2%). For the ITT-LOCF population, the mean change from baseline in the HAM-D17 total score was -4.76 (95% CI, -5.47 to -4.05). Continued numerical improvements in the HAM-D17 total scores and other depression outcome measures were observed irrespective of treatment in the previous study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clinical response				Secondary: Not reported
Soares et al.[45] (2011) Desvenlafaxine 100 to 200 mg/day	MC, OL Post-menopausal women 40 to 70 years of age with MDD who did not achieve clinical response to acute, DB treatment with desvenlafaxine or escitalopram	N=123 6 months	Primary: HAM-D-17 total score Secondary: CGI-I, HAMA, QIDS-SR, VAS-PI, MADRS, CSFQ, EQ-5D, health state today, MRS, SDS, treatment response (HAM-D-17 and MADRS based), safety	Primary: At final evaluation, mean reductions from acute-phase baseline HAM-D-17 total scores were -11.33 and -11.41 with desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine. Mean reductions from week eight of acute phase at the final evaluation of the OL extension phase were -6.13 and -6.59, respectively. Consistent improvements in mean HAM-D-17 total scores were observed among patients in both treatment groups from baselines of both the DB acute phase and the OL extension phase. Secondary: Improvements were demonstrated for additional efficacy and health outcome measures for patients in both groups during the OL extension phase. Throughout the course of the overall study, desvenlafaxine/ desvenlafaxine patients achieved mean improvements from baseline in CSFQ total scores after the acute phase and OL extension phase of 1.58±6.84 and 1.84±4.01, respectively; escitalopram/desvenlafaxine patients experienced improvements of 0.71±6.08 and 2.60±6.28 from respective baselines. HAM-D-17 response or remission rates after six months were achieved in 56 to 58 and 41 to 48% of desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine patients. MADRS response rates were 72 and 64%, respectively. The median time to remission was 68 (95% CI, 41 to 84) and 70 days (95% CI, 44 to 125) with desvenlafaxine/desvenlafaxine and escitalopram/ desvenlafaxine patients. Treatment-emergent adverse events were reported by 91% of patients, the most common being headache (17%), insomnia (17%), nausea (16%), dizziness (15%), infection (15%), abnormal dreams (12%), dry mouth (11%), pain (11%), and sweating (10%).
Ferguson et al.[46] (2010) Desvenlafaxine	MC, OL Outpatients ≥65 years of age with	N=52 (safety analysis)	Primary: Safety Secondary:	Primary: The most frequently reported adverse events were mild or moderate nausea (40%), dizziness (25%), and headache (21%). Primary and secondary adverse events led to discontinuation of treatment for 18 (35%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 or 200 mg/day	MDD	≤6 months	HAM-D-17 total scores	patients. The most common event cited as reasons for discontinuation were hypertension (10%) and nausea (10%). Two patients experienced three serious adverse events. Secondary: After three months of treatment, mean total HAM-D-17 score decreased 9.20 points (LOCF) from a baseline score of 21.68±3.20. This improvement was maintained for the duration of the trial; the mean change from baseline at final evaluation at month six was -9.28 points, resulting in a mean HAM-D-17 total score of 12.40±7.19. These improvements were maintained without dose escalation. HAM-D-17 based response rates were 42% (LOCF) at month three. The clinical responses were maintained by 65% of patients at month six. HAM-D-17 based remission rates were 28% at month two, which were maintained by 30% of patients at month six.
Soares et al.[47] (2010) Desvenlafaxine 100 to 200 mg/day vs escitalopram 10 to 20 mg/day	AC, DB, MC, RCT Postmenopausal women 40 to 70 years of age with MDD	N=607 Acute phase: 8 weeks Continuation phase: 6 months	Primary: HAM-D_{17} total score, response and remission rates, anxiety scores, QOL, menopause-related symptoms, safety and tolerability Secondary: Not reported	Primary: <u>Acute phase</u> There was no significant difference in HAM-D_{17} total score with desvenlafaxine and escitalopram (-13.63 vs -14.30, respectively; P=0.243). There were no significant differences in secondary efficacy and health outcomes data related to depression between treatment groups. On assessments of menopause-related symptoms, there were no significant between-group differences, and improvements from baseline were comparable for both groups. Significantly higher rates were found for escitalopram compared to desvenlafaxine for HAM-D_{17} remission (48 vs 38%, respectively; P<0.01) and response (73 vs 64%, respectively; P<0.05). No significant differences between the escitalopram and desvenlafaxine groups were observed in rates of response on the MADRS (70 and 67%, respectively) and CGI-I (75 and 70%, respectively). <u>Continuation phase</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The proportion of women who maintained or improved their HAM-D_{17} response to treatment was similar between the treatment groups (desvenlafaxine, 82%; escitalopram, 80%; P=0.702). There were no significant differences between treatment groups in the proportion of women who achieved HAM-D_{17} remission during the continuation phase or at endpoint (desvenlafaxine, 68%; escitalopram, 61%; P=0.234). There were no significant differences between the desvenlafaxine and escitalopram groups in rates of response on the MADRS (92 and 88%, respectively) and CGI-I (90 and 86%, respectively). No significant differences between groups were found at endpoint in the analyses of secondary efficacy data or core health outcome measures, including assessments of menopause-related symptoms. In both phases, desvenlafaxine and escitalopram were generally safe and well tolerated. Secondary: Not reported
Tabuteau et al.[48] (2022) Dextromethorphan-bupropion (45 mg/105 mg tablet) once daily for the first 3 days and twice daily thereafter vs bupropion (105 mg tablet) once daily	DB, MC, RCT Patients 18 to 65 years of age with a diagnosis of major depressive disorder of moderate or greater severity	N=80 6 weeks	Primary: Overall treatment effect on MADRS score (average of the change from baseline for weeks 1 to 6) Secondary: Clinical response (defined as a reduction ≥50% from baseline in MADRS total score); remission	Primary: The mean change from baseline in MADRS score over weeks one to six (overall treatment effect) was greater with dextromethorphan-bupropion than with bupropion (-13.7 points vs -8.8 points; least-squares mean difference, -4.9; 95% CI,-3.1 to -6.8; P<0.001). Secondary: Remission rates were significantly greater with dextromethorphan-bupropion at week two and every time point thereafter (week six: 46.5% vs 16.2%; least-squares mean difference, 30.3%; 95% CI,11.2 to 49.4; P=0.004). Response rates at week six were 60.5% with dextromethorphan-bupropion and 40.5% with bupropion (least-squares mean difference, 19.9%; 95% CI,-1.6 to 41; P=0.075). Most secondary outcomes favored dextromethorphan-bupropion. The most common adverse events with dextromethorphan-bupropion were dizziness, nausea, dry mouth,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for the first 3 days and twice daily thereafter			(defined as a MADRS total score ≤10); safety	decreased appetite, and anxiety. Dextromethorphan-bupropion was not associated with psychotomimetic effects, weight gain, or sexual dysfunction.
Iosifescu et al.[49] (2022) GEMINI Dextromethorphan-bupropion (45 mg/105 mg tablet) once daily for the first 3 days and twice daily thereafter vs placebo	DB, MC, RCT Patients 18 to 65 years of age with a primary diagnosis of MDD, experiencing a major depressive episode of at least four weeks in duration, and having a MADRS total score of 25 or higher, corresponding to moderate or greater severity	N=327 6 weeks	Primary: Change from baseline to week six in the MADRS total score Secondary: Change from baseline in the MADRS total score at week one; change from baseline in the MADRS total score at week two; remission, defined as MADRS total score ≤ 10, at week two; and clinical response, defined as ≥ 50% reduction in MADRS total score, at week six; safety	Primary: The least-squares mean change from baseline to week six in MADRS total score was −15.9 points in the dextromethorphan-bupropion group and −12.0 points in the placebo group (least-squares mean difference, −3.87; 95% CI, −1.39 to −6.36; P=0.002). Secondary: At week one, the first time point, the least-squares mean change from baseline in MADRS total score was −7.20 points in the dextromethorphan-bupropion group and −4.97 points in the placebo group (least-squares mean difference, −2.23; 95% CI, −0.60 to −3.86; P=0.007). At week two, the least-squares mean change from baseline in MADRS total score was −11.09 points in the dextromethorphan-bupropion group and −7.66 points in the placebo group (least-squares mean difference, −3.44; 95% CI, −1.40 to −5.47; P<0.001). Remission, defined as a MADRS total score of ≤ 10, was achieved by a significantly greater percentage of patients in the dextromethorphan-bupropion group than in the placebo group at week two (16.9% and 7.5%, respectively; treatment difference, 9.4%; 95% CI, 1.9% to 16.8%; P=0.013) and at every time point thereafter. At week six, the percentage of patients achieving clinical response was 54.0% in the dextromethorphan-bupropion group and 34.0% in the placebo group (treatment difference, 20.0%; 95% CI, 8.4% to 31.6%; P<0.001). The most common adverse events in the dextromethorphan-bupropion group were dizziness, nausea, headache, somnolence, and dry mouth. Dextromethorphan-bupropion was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.
Acharya et al.[50] (2006) Duloxetine 40 to 120 mg daily vs	MA (12 trials) Patients taking duloxetine for MDD	N=2,996 Duration varied	Primary: Incidence of suicide-related events with duloxetine (MHID, MHRD, HAM-D Item-3)	Primary: There were no significant differences in the incidence of suicide-related events with duloxetine vs placebo. The MHID for suicide-related behaviors was -0.03% (95% CI, -0.48 to 0.42) and MHRD -0.002 (95% CI, -0.02 to 0.02). Changes in HAM-D Item-3 suicidality scores showed a greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			Secondary: Not reported	improvement with duloxetine (P<0.001) and less worsening of suicidal ideation with duloxetine (P<0.001). Secondary: Not reported
Gaynor et al.[51] (2011) Duloxetine 60 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a current episode of MDD and at least moderate pain	N=528 8 weeks	Primary: Mean change in MADRS total score and BPI average pain rating Secondary: Remission, PGI-I, SDS global functional impairment score, safety	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to treatment with placebo (-16.77 vs -12.73, respectively; 57.9 vs 44.3% improvement from baseline, respectively; P<0.001). Duloxetine was more effective than placebo beginning at week two and at all remaining visits (P≤0.001). There was a significantly greater reduction in average pain rating from baseline to week eight with duloxetine compared to placebo (-1.93 vs -1.31, respectively; 35.1 vs 22.9% reduction in pain, respectively; P≤0.001). Patients also had a greater improvement in their average pain rating at weeks one, two, four, and eight with duloxetine compared to placebo (all P≤0.005). Secondary: A significantly greater proportion of patients receiving duloxetine met the criteria for remission than patients receiving placebo (P≤0.01). Overall scores for 'worst pain' and 'least pain' in the last 24 hours and for 'pain right now' were also reduced with duloxetine vs placebo (all P≤0.001). The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo (P≤0.021). Scores of 1 ('very much better') or 2 ('much better') were reported by a significantly greater percentage of patients in the duloxetine group (50.8%) compared to the placebo group (35.2%; P≤0.001). Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to patients receiving placebo (48.2 vs 37.7%, respectively; P=0.019). Improvements in the individual items addressing social life/leisure

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				activities and family life/home responsibilities were greater with duloxetine compared to placebo (P≤0.05). The improvement in the item addressing school/work life was not significantly different between duloxetine and placebo (P=0.112). Treatment emergent adverse events with duloxetine were nausea, somnolence, constipation, decreased appetite, and hyperhidrosis. Rates of discontinuation due to adverse events were greater for duloxetine than placebo (8.0 vs 3.4%, respectively; P=0.024).
Gaynor et al.[52] (2011) Duloxetine 60 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a current episode of MDD and at least moderate pain	N=527 8 weeks	Primary: Mean change in MADRS total score and BPI average pain rating Secondary: Remission, PGI-I, SDS global functional impairment score	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to treatment with placebo (-14.96 vs -10.77, respectively; 48.3 vs 34.8% improvement from baseline, respectively; P<0.001). There was a significantly greater reduction in average pain rating from baseline to week eight with duloxetine compared to placebo (-1.66 vs -1.17, respectively; 27.7 vs 18.9% reduction in pain, respectively; P<0.001). Patients also had greater improvement in their average pain rating at weeks two, four, and eight with duloxetine compared to placebo (all P<0.01). Secondary: A significantly higher percentage of patients receiving duloxetine (37.3%) met the criteria for remission compared to patients receiving placebo (23.0%; P<0.001). Greater improvements were observed for the other pain severity ratings (worst pain; P<0.001, least pain; P=0.003, pain right now; P<0.001), as well as ratings of interference of pain with functioning (all P<0.05) with duloxetine vs placebo. The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo (P≤0.01). Scores of 1 (‘very much better’) or 2 (‘much better’) were reported by a significantly greater percentage of patients in the duloxetine group compared to the placebo group (53.3 vs 26.8%, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to placebo (46.4 vs 31.8%, respectively; P<0.001).
Rosso et al.[53] (2012) Duloxetine 120 mg/day vs bupropion ER 300 mg/day	RCT, SB Patients ≥18 years of age with MDD who failed to respond to 2 consecutive antidepressant trials with SSRIs	N=49 6 weeks	Primary: Change in HAM-D-17 Secondary: CGI-S, GAF	Primary: There was no significant difference in HAM-D-17 total score among the treatment groups (P=0.793). Secondary: There was no significant difference in CGI-S (P=0.653) or GAF (P=0.565) scores among the treatment groups. Compared to baseline, there was a significant improvement in HAM-D-17 and CGI-S total scores with duloxetine and bupropion ER compared to baseline (all P<0.001). The 6-item-HAM-D mean score decreased significantly by week two with duloxetine (from 11.84 to 6.04; P<0.001) and bupropion ER (from 12.05 to 5.52; P<0.001). There was no difference in the success rates (HAM-D response, HAM-D remission) between the treatment groups. Additional information obtained by the CGI-S success rate confirmed this finding.
Nierenberg et al.[54] (2007) Duloxetine 60 mg daily vs escitalopram 10 mg daily vs placebo	AC, DB, PC, RCT Patients ≥18 years of age with MDD	N=547 8 weeks	Primary: Percentage of patients achieving onset criteria at week two (defined as 20% decrease from baseline in HAM-D) Secondary: Not reported	Primary: No significant difference was observed in the probability of patients meeting onset criteria at week two between the duloxetine group and the escitalopram group (P=0.097). Duloxetine and escitalopram both showed significant improvement compared to placebo on primary efficacy analysis at week one and week eight (P≤0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pigott et al.[55] (2007) Acute Phase Duloxetine 60 mg/day vs escitalopram 10 mg/day vs placebo Extension Phase Duloxetine 60 to 120 mg/day vs escitalopram 10 to 20 mg/day	DB, MC, PC, RCT Patients >18 years of age with MDD	N=684 Acute Phase 8 weeks Extension Phase 24 weeks	Primary: HAM-D_{17}, CGI-S, PGI-I, HAMA, remission rates Secondary: Not reported	Primary: After eight months of treatment, there were no significant differences in efficacy between duloxetine and escitalopram as assessed by mean changes from baseline in the HAM-D_{17} total score and the HAM-D_{17} Maier, anxiety/somatization, and retardation/ somatization subscales. The only HAM-D_{17} subscale with a significant drug difference was the HAM-D_{17} sleep subscale, which demonstrated that escitalopram was associated with a significantly greater improvement in insomnia than duloxetine at the eight-month study endpoint. There were no significant differences in efficacy among the treatment groups as assessed by the CGI-S and the PGI-I. After eight months of treatment, there were no significant differences between the treatment groups with regards to anxiety symptoms as measured by the HAMA total score and the HAMA subscales (psychic and somatic). There was no significant difference in remission at eight weeks (duloxetine 40%, escitalopram 33%; P=0.25) or at eight months (duloxetine 70%, escitalopram 75%; P=0.44). Secondary: Not reported
Detke et al.[56] (2004) Duloxetine 40 or 60 mg BID vs paroxetine 20 mg/day vs	DB, PC, RCT Outpatients ≥18 years of age with MDD	N=367 (acute phase) N=273 (continuation phase) 8 weeks of acute treatment plus a 6-month continuation	Primary: HAM-D-17 total scores Secondary: HAM-D-17 subscales, MADRS, HAMA, VAS for pain, CGI-S, PGI-I, SSI, SDS, safety	Primary: In the acute phase, patients treated with duloxetine had significantly greater improvement in HAM-D-17 total scores at week eight (P=0.001 and P<0.001) compared to patients treated with placebo. Paroxetine also demonstrated significant superiority over placebo at week eight (P<0.001). In the acute phase, estimated probabilities of response at week eight for patients receiving duloxetine 80 (70%) and 120 mg/day (77%) were significantly more efficacious to that of placebo (47%; P=0.005 and P<0.001). The estimated probability of response for paroxetine-treated patients was also significantly greater compared to placebo-treated patients (P<0.001).

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placebo After acute treatment, patients who had a ≥30% reduction in baseline HAM-D-17 total score were allowed to continue on the same (blinded) treatment for a 6-month continuation phase.		phase		In the acute phase, estimated probabilities of remission for patients receiving duloxetine 80 and 120 mg/day, and paroxetine 20 mg/day were significantly more efficacious to patients receiving placebo at week eight. In the continuation phase, patients within each active treatment group demonstrated significant within-group improvement in HAM-D-17 total score. In the continuation phase, a log-rank test demonstrated that duloxetine 80 mg/day, duloxetine 120 mg/day, and paroxetine each had a significantly longer time to loss of response compared to placebo (P=0.002, P=0.018, and P=0.002, respectively). Secondary: In the acute phase, duloxetine 80 mg/day, duloxetine 120 mg/day, and paroxetine showed significantly greater improvement on the HAM-D-17 anxiety/somatization, core factor, maier, and retardation subscales compared to placebo. Paroxetine-treated patients showed a significant improvement on the sleep subscale compared to patients receiving placebo. In the acute phase, patients receiving duloxetine 80 mg/day, duloxetine 120 mg/day, or paroxetine 20 mg/day has significantly greater improvements in MADRS (P≤0.001 vs placebo for all, P≤0.05 for duloxetine 120 vs 80 mg/day), HAMA (P≤0.01 for duloxetine 80 mg/day vs placebo, P≤0.001 for duloxetine 120 mg/day and paroxetine vs placebo), CGI-S (P≤0.001 for all comparisons), and PGI-I (P≤0.01 for duloxetine 80 mg/day vs placebo, P≤0.001 for duloxetine 120 mg/day and paroxetine vs placebo, P≤0.05 for duloxetine 80 mg/day vs paroxetine) scales compared to patients receiving placebo. In the acute phase, patients receiving duloxetine or paroxetine showed significantly greater improvement on both SSI 26- and 28-Item Averages compared to placebo-treated patients. Using mean change analysis, in the acute phase patients treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				duloxetine and paroxetine showed significantly greater improvement on the SDS work item, social life item, family life item, and total score compared to patients receiving placebo. In the continuation phase, patients within each active treatment group demonstrated significant within-group improvement in MADRS, HAMA, CGI-S, and PGI-I. Patients receiving placebo exhibited significant within-group improvement in HAMA and PGI-I. In the continuation phase, patients receiving duloxetine 120 mg/day showed marginally significant improvement from baseline on the SSI 28-Item Average (P=0.054), while improvement was significant for the Pain Item Average (P=0.034). There were no deaths during the acute treatment phase. One serious adverse event occurred in a patient receiving paroxetine, but was considered to be non-treatment related. The proportion of patients who discontinued the study due to adverse events did not differ significantly across treatment groups (4.2, 3.2, 3.5, and 3.2%; P=1.00). The only adverse event leading to discontinuation in more than one patient within any treatment group was headache (two patients receiving duloxetine 120 mg/day). Treatment-emergent adverse events experienced by ≥5% of patients receiving duloxetine 120 mg/day are constipation, dry mouth, increased sweating, somnolence, nausea, headache, and insomnia. Three patients died during the six-month continuation phase (one patient receiving duloxetine 120 mg/day and placebo died as a result of suicide, while one patient receiving duloxetine 80 mg/day died as a result of pulmonary edema). All three deaths were considered to be non-treatment related. Serious adverse events were reported by one placebo-treated patient, one duloxetine 80 mg/day-treated patient, and four duloxetine 120 mg/day-treated patients. The proportions of patients discontinuing treatment due to an adverse event were similar across groups.
Goldstein et al.[57] (2004) Duloxetine 20 to	DB, PC, RCT Outpatients with depression	N=353 8 weeks	Primary: HAM-D Secondary:	Primary: Duloxetine 80 mg/day was more effective than placebo on mean HAM-D-17 total change by 3.62 points (95% CI, 1.38 to 5.86; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40 mg BID vs paroxetine 20 mg daily vs placebo			Adverse effects	Duloxetine 40 mg/day was also significantly more efficacious than placebo by 2.43 points (95% CI, 0.19 to 4.66; P=0.034), while paroxetine was not (1.51 points; 95% CI, -0.55 to 3.56; P=0.150). Duloxetine 80 mg/day was more efficacious than placebo for most other measures, including overall pain severity, and was more efficacious than paroxetine on the HAM-D-17 improvement (by 2.39 points; 95% CI, 0.14 to 4.65; P=0.037) and estimated probability of remission (57% for duloxetine 80 mg/day, 34% for paroxetine; P=0.022). Secondary: The only adverse event reported significantly more frequently for duloxetine 80 mg/day than for paroxetine was insomnia (19.8% for duloxetine 80 mg/day, 8.0% for paroxetine; P=0.031).
Perahia et al.[58] (2006) Duloxetine 40 mg BID vs duloxetine 60 mg BID vs paroxetine 20 mg daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with MDD	N=392 8 months	Primary: Mean change from baseline in HAM-D-17 Secondary: Discontinuation of study drug due to adverse drug events	Primary: Patients treated with duloxetine 80 and 120 mg/day had significantly greater improvement in HAM-D-17 total scores at week eight compared to placebo-treated patients (P=0.045 and P=0.014, respectively). Paroxetine was not significantly different from placebo (P=0.089) on mean change on the HAM-D-17. Secondary: The proportion of patients who discontinued the study due to adverse events did not differ significantly (P=0.836) across treatment groups; placebo (2.0%), duloxetine 80 mg/day (4.3%), duloxetine 120 mg/day (3.9%), and paroxetine 20 mg (4.1%).
Goldstein et al.[59] (abstract) (2002)	DB, MC, PC, RCT Patients 18 to 75 years of age with	N=173 8 weeks	Primary: HAM-D-17 total score	Primary: Duloxetine was more efficacious to placebo in change in HAM-D-17 total score (P=0.009). Estimated probabilities of response and remission were 64 and 56%, respectively, with duloxetine compared to 52 and 30% with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duloxetine, titrated from 20 to 60 mg BID vs placebo vs fluoxetine 20 mg/day	MDD		Secondary: MADRS, CGI-S, CGI-I, PGI-I, safety	fluoxetine, and 48 and 32% with placebo. Duloxetine was numerically more efficacious to fluoxetine on the primary outcome. Secondary: Duloxetine was numerically more efficacious to fluoxetine on most secondary outcomes. Duloxetine was well tolerated; 76% of patients achieved the maximum dose, and insomnia and asthenia were the only adverse events reported significantly more frequently compared to placebo (P<0.05).
Martinez et al.[60] (2012) Duloxetine 30 to 120 mg QD vs generic SSRIs (citalopram 20 to 40 mg/day, fluoxetine 20 to 80 mg/day, paroxetine 20 to 50 mg/day, or sertraline 50 to 200 mg/day at the investigator's discretion)	AC, MC, RCT Adult outpatients with severe MDD	N=750 12 weeks	Primary: Remission at week 12 as measured by QIDS-SR Secondary: Response as measured by QIDS-SR, probability of response and remission as measured by HAM-D_{17}, BPI, SDS	Primary: Remission rates derived from the QIDS-SR at week 12 did not significantly differ between the duloxetine and SSRI treatment groups (36 vs 32%, respectively). The groups did not differ significantly with respect to changes in QIDS-SR scores across 12 weeks of therapy. Secondary: The QIDS-SR estimated probability of response did not differ significantly between duloxetine-treated and SSRI-treated patients (71 vs 64%; P=0.085). On the HAM-D_{17}, patients treated with duloxetine had significantly greater probabilities of response compared to patients treated with SSRIs (73 vs 61%; P=0.001) and remission (53 vs 44%; P=0.034). The NNT for one additional case of remission was 25 for the QIDS-SR, and was 12 for the HAM-D_{17}. The NNT for one additional case of response was 15 for the QIDS-SR, and was 9 for the HAM-D_{17}. Patients treated with duloxetine demonstrated significantly greater mean changes on the HAM-D_{17} total score and HAM-D subscales (anxiety/ somatization, Bech, Maier, and retardation). Improvement in associated painful symptoms was significantly greater with duloxetine compared to SSRIs as measured by the mean change in the BPI 24-hour average pain score in both the pain-enriched cohort of patients (P=0.034) and in the entire study population (P=0.030).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients receiving duloxetine demonstrated significantly greater improvements on the SDS global functional score (P=0.002), and on each of the individual items that measure work/school (P=0.013), family functioning (P=0.015), and social functioning (P=0.005) compared to SSRIs. Dry mouth and constipation occurred at a significantly greater rate in patients treated with duloxetine vs patients treated with SSRIs (P=0.023 and 0.003, respectively). There was no significant difference between duloxetine and the SSRI group in the occurrence of any of the other most commonly reported treatment emergent adverse events.
Mancini et al.[61] (2012) Duloxetine vs placebo	MA (6DB, PC, PG, RCT) Patients with MDD	N=2,496 Short-term (7 to 13 weeks) and the long-term (>24 weeks) endpoint	Primary: SDS total score Secondary: Functional remission (SDS total< 6) rates, VAS	Primary: The between-treatment difference of -2.52 between duloxetine and placebo in the SDS total score at the short-term endpoint was statistically significant in favor of duloxetine vs placebo (95% CI, -3.17, -1.87; P<0.001). Secondary: The endpoint functional remission rates were 39.5% with duloxetine and 28.7% with placebo. Time since first depression episode, antidepressant pretreatment (yes/no), baseline VAS pain (<30/>30 mm), and sex were significant prognostic factors. The effect of duloxetine was maintained at the long-term endpoint.
Van Baardewijk et al.[62] (2005) Duloxetine 40 to 120 mg daily for at least 8 weeks vs venlafaxine ER 75 to 225 mg daily for at least 8 weeks	MA Adults with moderate to severe MDD and a score ≥15 on the HAM-D or ≥18 on the MADRS scale	N=not specified 6 months	Primary: Remission (an improvement in the HAM-D scale to a score <7, or a score ≤10 on the MADRS scale), symptom-free days Secondary: Not reported	Primary: Patients receiving duloxetine and venlafaxine ER experienced similar success rates after six months of treatment, 53 and 57%, respectively (P value not reported). Patients receiving duloxetine and venlafaxine ER experienced similar number of symptom-free days after six months of treatment, 52.72 and 57.03%, respectively (P value not reported). Duloxetine therapy was associated with a greater hospitalization rate compared to venlafaxine ER therapy, 47 and 43%, respectively (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Vis et al.[63] (2005) Duloxetine 40 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	MA (8 trials) Outpatients >18 years of age with MDD	N=1,754 (efficacy) N=1,791 (safety) 8 weeks	Primary: Remission and response (HAM-D, MADRS) Secondary: Dropout rates and rates of adverse events	Primary: Both treatment groups demonstrated a significant difference compared to placebo for both remission and response (P<0.001 for all). Secondary: More patients receiving placebo dropped out due to lack of efficacy compared to patients in the treatment arms (P<0.001 for both drugs). Dropout rates due to adverse reactions were also significant when active drugs were compared to placebo (P value not reported). More patients in the treatment groups than in the placebo groups dropped out due to adverse reactions (venlafaxine ER; P<0.001 and duloxetine; P=0.008).
Perahia et al.[64] (2008) Duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day	DB, MC, RCT (pooled analysis of 2 trials) Patients >18 years of age with MDD	N=667 12 weeks	Primary: GBR (remission at endpoint using HAM-D-17 ≤7) Secondary: Efficacy	Primary: There were no significant differences in GBR with duloxetine and venlafaxine ER at the end of six weeks of therapy (-1.418 vs -1.079; P=0.217) or 12 weeks (-0.349 vs -0.121; P=0.440). Secondary: Mean changes from baseline to endpoint in the HAM-D-17 total scores were not different between the duloxetine and venlafaxine ER treatment groups. Comparisons of mean change from baseline to endpoint on secondary efficacy measures (HAM-D-17 item 1, HAM-D-17 subscales [core, Maier, anxiety/somatization, retardation and sleep], HAMA total score, CGI-S, and PGI-I) were not significantly different between the treatment groups. Response and remission rates were not significantly different between duloxetine and venlafaxine ER at six weeks (response rate for duloxetine, 51.6%; venlafaxine, 54.5%; remission rate for duloxetine, 31.4%; venlafaxine, 35.2%) or 12 weeks (response rate for duloxetine, 62.6%; venlafaxine, 69.1%; remission rate for duloxetine, 48.1%; venlafaxine, 50.3%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Estimates of remission rates at two, four, eight and 12 weeks were 11.1, 36.6, 53.0, and 71.0% for the duloxetine-treated group and 10.4, 32.1, 51.7, and 67.4% for the venlafaxine-treated group, respectively (P=0.309).
Rush et al.[65] CO-MED (2011) Escitalopram 10 to 20 mg/day and placebo vs bupropion SR 300 to 400 mg/day and escitalopram 10 to 20 mg/day vs venlafaxine XR 150 to 300 mg/day and mirtazapine 15 to 45 mg/day	MC, PC, RCT, SB Patients 18 to 75 years of age with MDD	N=665 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	Primary: At 12 weeks, the remission rates were 38.8% for escitalopram plus placebo, 38.9% for bupropion SR plus escitalopram, and 37.7% for venlafaxine ER plus mirtazapine. The response rates were 51.6 to 52.4%. The treatment groups did not differ in the percentage of change in QIDS-SR score or in effects on QOL. At seven months, the treatment groups were not different in terms of remission rate (range, 41.8 to 46.6%), response rate (range, 57.4 to 59.4%), or attrition rate. There was no difference in the percentage of change in QIDS-SR, QOL, or work and social adjustment. The venlafaxine ER plus mirtazapine group had greater side effect frequency and intensity at 12 weeks and greater side effect frequency, intensity, and burden at seven months as compared to escitalopram plus placebo. Secondary: Not reported
Kerber et al.[66] CO-MED (2012) Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without heart disease	N=665 (6% [n=40] reported having and being treated for heart disease) 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	Primary: In general, patients with heart disease had fewer problems with treatment side effects at week 12 compared to patients without heart disease. At week 12, there were no significant differences between those with and without heart disease in terms of remission, response, QOL, or functional measures. This pattern was also seen with regard to measures at trial end (week 28). There were no significant differential treatment effects among those with and without heart disease in side effect burden and symptom severity at weeks 12 and 28.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day				Secondary: Not reported
Morris et al.[67] CO-MED (2012) Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without general medical conditions	N=665 (49.5% reported having no treated general medical conditions, 23.8% reported having 1, 14.8% reported having 2, and 11.9% reported having ≥3) 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	Primary: No differences in outcomes between antidepressant monotherapy and either of the antidepressant combination therapies, regardless of the number of general medical conditions a patient had. Specifically, within each group having a given number of conditions, the three treatments did not differ significantly with respect to any of the measures of efficacy or tolerability assessed, either at week 12 or 28. Secondary: Not reported
Moore et al.[68] (2005) Escitalopram 20 mg daily vs	DB, MC, RCT Outpatients with MDD having an MADRS score of ≥30 at baseline	N=280 8 weeks	Primary: Change from baseline in the MADRS total score, adverse events, response to treatment, remission rate	Primary: Escitalopram group exhibited a greater improvement in the MADRS score compared to the citalopram arm (–22.4 vs –20.3; P<0.05). There were more treatment responders with escitalopram than with citalopram (76.1 vs 61.3%; P<0.01). Remission rate was higher among patients on escitalopram compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
citalopram 40 mg daily			Secondary; Not reported	the citalopram group (56.1 vs 43.6%; P<0.05). Tolerability was similar in both treatment groups. Secondary; Not reported
Colonna et al.[69] (2005) Escitalopram 10 mg daily vs citalopram 20 mg daily	DB, RCT Patients with moderate-to-severe MDD	N=357 24 weeks	Primary: Change from base-line in MADRS Secondary: Change from baseline in CGI-S	Primary: No significant difference was observed between groups in the MADRS at week 24. Secondary: Escitalopram patients had significantly better scores on the CGI-S at week 24 compared to citalopram patients.
Burke et al.[70] (2002) Escitalopram 10 mg daily vs escitalopram 20 mg daily vs citalopram 40 mg daily vs placebo	DB, MC, RCT Outpatients 18 to 65 years of age with MDD	N=491 8 weeks	Primary: Change from baseline in the MADRS total score at week eight Secondary: Change from baseline in the MADRS total score at weeks one, two, four, and six, change from baseline in the HAM-D, CGI-S, CGI-I, HAMA, QOL, and CES-D	Primary: Mean changes from baseline for the MADRS score were significantly greater compared to placebo in the two escitalopram groups (P<0.01) and in the citalopram group (P<0.05). There were no significant differences in the mean change of MADRS score from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). Secondary: Patients randomized to the two escitalopram groups and the citalopram arm exhibited significantly greater improvement in the HAM-D score from baseline compared to placebo (P<0.01 and P<0.05, respectively). Response to treatment was observed in 50% of escitalopram 10 mg, 51.2% of escitalopram 20 mg, and 45.6% of citalopram 40 mg groups; the difference in response rate was significantly greater than that of placebo group (P<0.01) but not statistically different among the three active groups. There were no significant differences in the mean change of CGI-I, HAM-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				D, and CGI-S scores from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). All three treatment groups exhibited significantly improved HAM-D depressed mood scores from baseline to endpoint (P<0.01). Patients randomized to the escitalopram 10 and 20 mg group exhibited significantly greater improvement in the HAMA score from baseline compared to placebo (P=0.04 and P<0.01, respectively). Mean changes from baseline for the QOL score were significantly greater compared to placebo in the escitalopram 10 mg group (P=0.04) and in the escitalopram 20 mg group (P<0.01). Mean changes from baseline for the CES-D score were significantly greater compared to placebo in the escitalopram 10 mg group (P=0.02) and in the escitalopram 20 mg group (P<0.01). There was no statistically significant difference in the discontinuation rates due to adverse events between the escitalopram 10 mg and placebo groups; however, escitalopram 20 mg and citalopram 40 mg groups had significantly greater discontinuation rates compared to placebo (P<0.05). The rate of adverse effects was not significantly different between the escitalopram 10 mg group and placebo (79 vs 70.5%; P=0.14). Escitalopram 20 mg and citalopram 40 mg groups were associated with significantly greater adverse event rates compared to placebo (85.6 vs 86.4%; P<0.01).
Yevtushenko et al.[71] (2007) Escitalopram 10 mg/day vs	AC, DB, MC, RCT Patients 25 to 45 years of age with MDD	N=330 6 weeks	Primary: MADRS total score Secondary: MADRS total score in severely depressed patients,	Primary: The mean changes in MADRS total score were significantly greater in patients receiving escitalopram than citalopram 10 or 20 mg (-28.70 vs -20.11 and -25.19; both, P 0.001). The difference between the two citalopram groups was also significant (P<0.001). Secondary: In the severely depressed subpopulation, the differences in the mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
citalopram 10 mg/day vs citalopram 20 mg/day			MADRS core depression subscale score, CGI-S and CGI-I scores, proportions of patients classified as responders and remitters	change in MADRS score between the escitalopram group and the citalopram 10 and 20 mg groups were -9.46 and-3.99, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was -5.47 (P<0.001). The differences in mean change in MADRS core depression subscale scores between the escitalopram group and citalopram 10 and 20 mg groups were -6.00 and -2.48, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was -3.52 (P<0.001) The mean changes in CGI-S score were -2.60, -1.61, and -2.05 in the escitalopram, citalopram 10 mg, and citalopram 20 mg groups, respectively (all, P<0.001 vs baseline). The differences in mean changes from baseline between the escitalopram and citalopram 10 and 20 mg groups were -0.99 and -0.55, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was significant at end point (-0.44; P<0.001). Response rates were 95.4 vs 44.3 and 83.3% in the escitalopram vs citalopram 10 and 20 mg groups, respectively (both, P<0.001). Remission rates were 89.8 vs 25.5 and 50.9% in the escitalopram vs citalopram 10 and 20 mg groups, respectively (both, P<0.001).
Lam et al.[72] (2006) Escitalopram 10 to 20 mg daily vs citalopram 20 to 40 mg daily	MA Outpatients with MDD	N=1,321 (3 trials) 8 weeks	Primary: MADRS, response rate Secondary: CGI-I, CGI-S, HAM-D	Primary: No significant difference in response rate between the two treatment groups was seen at week eight. The analysis of pooled data demonstrated that the difference between citalopram and placebo was approximately constant; however, the difference between escitalopram and placebo (P=0.0010) and escitalopram and citalopram (P=0.0012) became greater the more severely depressed the patient was at baseline. Secondary: Similar results were seen in the secondary outcomes.
Gorman et al.[73] (2002)	MA	N=1,321 (3 trials)	Primary: MADRS, CGI-I	Primary: Mean change in MADRS score from baseline at week eight was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Escitalopram 10 to 20 mg daily vs citalopram 20 to 40 mg daily	Outpatients with MDD	8 weeks	Secondary; Not reported	significantly improved in both treatment groups compared to baseline (P<0.05). Mean change in MADRS score from baseline at week eight was significantly improved in the escitalopram group compared to the citalopram group (P<0.05). Mean change in CGI-I score from baseline at week eight was significantly improved in both treatment groups compared to baseline (P<0.05). No significant difference in CGI-I scores between the two treatment groups was reported at week eight (P>0.05).
Llorca et al.[74] (2005) Escitalopram 10 to 20 mg daily vs citalopram 20 to 40 mg daily vs placebo	MA Patient 18 to 80 years of age with depression	N=506 (3 trials) 8 weeks	Primary: MADRS Secondary: HAM-D, CGI-I, CGI-S	Primary: Mean change from baseline in MADRS total scores was significantly higher in the escitalopram-treated group compared to the citalopram-treated group (P=0.003). Response rates to escitalopram were 56% compared to 41% with citalopram (P=0.007). Secondary: The mean change in HAM-D from baseline between escitalopram and citalopram was in favor of escitalopram at endpoint (P=0.007). On both the CGI-I and CGI-S scales, patients showed a significant improvement at treatment endpoint in favor of escitalopram when compared to citalopram treatment (P=0.01 and P=0.001 for CGI-I and CGI-S, respectively).
Ou et al.[75] (2011) Escitalopram 10 to 20 mg/day vs citalopram 20 to	DB, MC, RCT Patients 18 to 65 years of age with MDD	N=240 6 weeks	Primary: Change in HAM-D_{17} total score Secondary: Response and remission rates	Primary: At all time-points, there was no significant difference in HAM-D_{17} total score, score change, or rate change among the treatment groups (all P>0.05). At the end of the study, the mean rate change was 62.5% in the escitalopram group and 60.7% in the citalopram group (P=0.653). Secondary: Overall, response rates were 72.17% with escitalopram compared to 74.36% with citalopram (P=0.707). Remission rates were 60.87% with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40 mg/day				escitalopram compared to 56.41% with citalopram (P=0.982). For severe MDD patients, response rates were 72.50 vs 71.79% with escitalopram and citalopram, respectively (P=0.991). Remission rates were 57.50 and 46.15% with escitalopram and citalopram, respectively (P=0.350). There was no significant difference in adverse events with escitalopram and citalopram (28.7 vs 29.9%, respectively; P=0.8384). Nausea and other gastrointestinal reactions (including stomach discomfort, burning sensation) were the most frequently reported adverse events. No serious adverse events were observed.
Wade et al.[76] (2007) Escitalopram 20 mg/day vs duloxetine 60 mg/day	DB, RCT Patients 18 to 65 years of age with MDD	N=294 24 weeks	Primary: Mean change in MADRS total score from baseline to week 24 Secondary: MADRS total score, HAM-D_{17}, CGI‑I, CGI‑S, HAMA scores	Primary: The mean change from baseline in MADRS total scores was –23.4 for escitalopram-treated patients and –21.7 for duloxetine treated patients (P=0.055). Secondary: At week eight, the mean change from baseline in MADRS total scores was –19.5 for escitalopram-treated patients and –17.4 for duloxetine-treated patients (P<0.05). There was no significant difference in the mean change from baseline in HAM-D_{17} (7.13 vs 8.47; P=0.096), HAMA (7.73 vs 8.62; P=0.267), CGI-I (1.76 vs 1.99; P=0.077), CGI-S (2.11 vs 2.28; P=0.214) at 24 weeks between escitalopram-treated patients and duloxetine-treated patients.
Khan et al.[77] (2007) Escitalopram 10 to 20 mg daily vs duloxetine 60 mg daily	DB, MC, PG, RCT Patients with MDD	N=278 8 weeks	Primary: Change from base-line to week eight in MADRS scores using the LOCF Secondary: Not reported	Primary: At week eight, a significantly greater decrease in MADRS scores (LOCF) was observed in the escitalopram group compared to the duloxetine group (P<0.05). No significant differences in MADRS scores were observed between groups in the observed case analysis (P=0.79). Secondary: Not reported
Boulenger et al.[78]	DB, MC, RCT	N=459	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Escitalopram 20 mg daily vs paroxetine 40 mg daily	Patients with MDD	24 weeks	Change in MADRS score, withdrawal Secondary: HAMA, CGI-S, remitters	The difference in MADRS scores at 24 weeks compared to baseline was -25.2 for the escitalopram treated patients compared to -23.1 for the paroxetine-treated patients (P=0.0105). Significantly more patients withdrew from the study in the paroxetine group (32%) compared to the escitalopram group (19%; P<0.05). Secondary: The difference in HAMA scores at 24 weeks compared to baseline was –15.1 for the escitalopram-treated patients compared to –13.2 for the paroxetine-treated patients (P=0.01). The difference in CGI-S scores at 24 weeks compared to baseline was –2.8 for the escitalopram-treated patients compared to –2.6 for the paroxetine-treated patients (P=0.05). After 24 weeks of treatment the proportion of remitters was 75% in the escitalopram group compared to 66.8% in the paroxetine group (P<0.05).
Montgomery et al.[79] (2004) Escitalopram 10 to 20 mg daily vs venlafaxine ER 75 to 150 mg daily	DB, RCT Patients with MDD	N=293 8 weeks	Primary: Change from baseline in MADRS scores Secondary: Not reported	Primary: No significant difference between groups was observed at week eight in MADRS scores. Escitalopram-treated patients achieved remission significantly faster compared to venlafaxine patients in a post-hoc analysis. Secondary: Not reported
Fedgchin et al.[80] (2019) TRANSFORM-1 Esketamine nasal spray 56 mg or 84 mg twice weekly	AC, DB, MC, RCT Patients 18 to 64 years of age with recurrent MDD or single-episode MDD (≥2 years), without psychotic	N=346 4 weeks	Primary: Change from baseline (day 1) to day 28 in MADRS total score Secondary: Onset of clinical	Primary: Statistical significance was not achieved with esketamine 84 mg compared with placebo (LS means difference [95% CI]: -3.2 [-6.88 to 0.45]; 2-sided P value=0.088). Although esketamine 56 mg could not be formally tested, the LS means difference was -4.1 [-7.67 to -0.49] (2-sided P value=0.027). Secondary: Results of onset of clinical response by day 2, SDS total score, and PHQ-9

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	features		response by day 2 (24 hours) that was maintained until day 28, change from baseline in SDS and PHQ-9 total score at day 28, proportion or responders and remitters	total score numerically favored both the esketamine treatment groups over placebo group. The onset of clinical response by day 2 maintained to day 28 was achieved by 12 subjects (10.4%), 10 subjects (8.8%) and 2 subjects (1.8%) in the esketamine 56 mg, esketamine 84 mg and placebo group, respectively. The difference in response rates in the esketamine 56 mg group compared to placebo was 8.90 (OR=6.47; 95% CI, 1.38 to 60.45) and in the esketamine 84 mg compared to placebo was 6.76 (OR=5.34; 95% CI, 1.09 to 50.91). The difference of LS means for the change in baseline in SDS in the esketamine 56 mg group compared to placebo was -2.5 (95% CI, -5.25 to 0.20) and in the esketamine 84 mg group was -2.2 (95% CI, -4.91 to 0.53). The difference of LS means for the change in baseline in PHQ-9 total in the esketamine 56 mg group compared to placebo was -2.3 (95% CI, -4.34 to -0.31) and in the esketamine 84 mg group was -2.2 (95% CI, -4.26 to -2.0). The proportion of patients who were responders and the proportion in remission at any given timepoint generally increased over the double-blind phase in all 3 treatment groups; at day 28, a total of 54.1%, 53.1%, and 38.9% of patients in the esketamine 56 mg, esketamine 84 mg, and placebo groups, respectively, were responders, and 36.0%, 38.8%, and 30.6%, respectively, were in remission.
Popova et al.[81] (2019) TRANSFORM-2 Esketamine nasal spray 56 mg or 84 mg twice weekly plus a new oral antidepressant once daily vs	DB, flexible-dose, MC, PC, RCT Patients 18 to 64 years of age with a diagnosis of single-episode (≥2 years) or recurrent MDD without psychotic features, a total score ≥34 on IDS-C30 (moderate-to-	N=223 4 weeks	Primary: Mean change in MADRS total score from baseline to day 28 Secondary: Proportion of responders (≥50% reduction from baseline in MADRS total	Primary: Patients treated with esketamine nasal spray plus an oral antidepressant demonstrated greater improvements from baseline to endpoint in mean MADRS total score compared to those treated with placebo plus an oral antidepressant (-19.8 vs -15.8; LSMD, -4.0; 95% CI, -7.31 to -0.64; P=0.020). Secondary: At the study endpoint, 69.3% of patients treated with esketamine achieved clinical response compared to 52.0% of patients treated with placebo. In addition, 52.5% of patients treated with esketamine achieved clinical remission compared to 31.0% of patients treated with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo nasal spray twice weekly plus a new oral antidepressant once daily	severe), non-response to ≥2 AD in the current episode of depression (treatment resistant)		score) at day 28, proportion of patients in remission (MADRS total score ≤12) at day 28, change in SDS total score from baseline to day 28, change in PHQ-9 total score from baseline to day 28, CGI-S	The percentage of patients who experienced sustained clinical response (from day two to 28) was 7.9% in those treated with esketamine, compared to 4.6% in the placebo group. The between-group difference was not statistically significant (P=0.321); therefore, endpoints related to SDS (-12.3 vs -8.4; LSMD, -4.0; 95% CI, -6.28 to -1.64), PHQ-9 (-11.8 vs -9.4; LSMD, -2.4; 95% CI, -4.18 to -0.69), and CGI-S (-2 vs -2; OR, 2.8; 95% CI, 1.14 to 7.68) could not be formally evaluated.
Daly et al.[82] (2019) SUSTAIN-1 Esketamine nasal spray 56 mg or 84 mg twice weekly plus a new oral antidepressant once daily vs placebo nasal spray twice weekly plus a new oral antidepressant once daily	DB, flexible-dose, MC, RCT, WD Patients 18 to 64 years of age with a diagnosis of single-episode (≥ 2 years) or recurrent MDD without psychotic features, a total score ≥34 on IDS-C30 (moderate-to-severe), non-response to ≥2 AD in the current episode of depression	N=297 16 weeks	Primary: Mean time to relapse in stable remitters (defined as MADRS total score ≥22 for two consecutive assessments separated by five to 15 days, hospitalization for worsening depression, suicide attempt, suicide prevention or completed suicide, or any other clinically relevant event suggestive of relapse) Secondary: Time to relapse in patients with a	Primary: Among stable remitters, 26.7% of patients treated with esketamine plus an oral antidepressant experienced a relapse event compared to 45.3% of patients treated with placebo. Secondary: Treatment with esketamine significantly delayed time to relapse by 51% among patients achieving stable remission compared to placebo (HR, 0.49; 95% CI, 0.29 to 0.84; P=0.003). Among stable responders, 25.8% of patients treated with esketamine plus an oral antidepressant experienced a relapse event, compared to 57.6% of patients treated with placebo. Treatment with esketamine significantly delayed relapse by 70% compared to placebo (HR, 0.30; 95% CI, 0.16 to 0.55; P<0.001). Median time to relapse was 635 days for those treated with esketamine, compared to 88 days for those treated with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			stable response, change from baseline to the maintenance phase endpoint for PHQ-9, SDS, and CGI-S	
Davey et al.[83] (2019) YoDA-C study Fluoxetine 20 to 40 mg QD* vs placebo* *Given in combination with cognitive behavioral therapy	DB, MC, PC, PG, RCT Patients 15 to 25 years of age with moderate-to severe MDD and scored ≥20 on MADRS	N=153 12 weeks	Primary: Change in MADRS score at 12 weeks Secondary: QIDS, GAD-7, Suicidal Ideation Questionnaire, Social and Occupational Functioning Assessment Scale and Quality of Life Enjoyment and Satisfaction Questionnaire–Short-Form	Primary: After 12 weeks of treatment both groups showed a reduction in MADRS scores (-13.7; 95% CI, -16.0 to -11.4, in the placebo group and -15.1; 95% CI, -17.4 to -12.9, in the fluoxetine group). There was no significant between-group difference in change in MADRS score at 12 weeks. (mean difference: -1.4; 95% CI, -4.7 to 1.8; P=0.39). Secondary: There was no significant between-group difference for changes in self-reported depressive symptoms, measured with the QIDS (-1.0; 95% CI, -2.7 to 0.7; P=0·26). There was evidence of a greater reduction in anxiety symptoms, as measured by the GAD-7, in the fluoxetine group compared with the placebo group (-2.1; 95% CI, -3.9 to -0.3; P=0.02). During the 12 weeks of the trial, there were five suicide attempts in the placebo group and one in the fluoxetine group. There were no significant differences observed between the groups on the Suicidal Ideation Questionnaire. Changes in functioning, as measured using the Social and Occupational Functioning Assessment Scale, and quality of life, as measured using Quality of Life Enjoyment and Satisfaction Questionnaire–Short-Form, did not differ between the groups after 12 weeks of treatment for individuals <18 years of age; however there was evidence of greater improvement in the fluoxetine group compared to the placebo group for individuals >18 years of age.
Fava et al.[84] (2002)	DB, MC, RCT Patients ≥18 years	N=284 10 to 16 weeks	Primary: HAM-D_{17} scores	Primary: As indicated by baseline-to-endpoint improvement on the HAM-D_{17}, there were no statistically significant differences between fluoxetine, sertraline,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluoxetine 20 mg daily vs sertraline 50 mg daily vs paroxetine 20 mg daily	of age with depression		Secondary: Improvement in insomnia/sleep disturbances	and paroxetine on all outcome measures (P=0.365). Secondary: Insomnia improvement when using the sleep disturbance factor was similar in all patients with no significant difference between groups (P=0.868).
Thase et al.[85] (2002) Imipramine (mean dosage, 221 mg/day) vs sertraline (mean dosage, 163 mg/day)	DB, SC Patients with chronic major depression who failed to respond to 12 weeks of treatment with either imipramine or sertraline	N=168 12 weeks	Primary: HAM-D, CGI Secondary; Not reported	Primary: The two groups were equal in response rates for completers, 63 and 55% for the sertraline and imipramine groups, respectively (P=0.16). However, in the ITT analysis there was a statistically better outcome for the sertraline group (P=0.03). Those patients going from sertraline to imipramine experienced significant increases in eight adverse events and significant reductions in three adverse events while those patients going from imipramine to sertraline experienced a significant reduction in seven adverse events and no increase in any adverse event. Secondary; Not reported
Le Noury et al.[86] (2015) Study 329 Imipramine (200 to 300 mg/day) vs paroxetine (20 to 40 mg/day)	Reanalysis of DB, MC, PC, RCT Adolescents 12 to 18 years of age who met DSM-IV criteria for a current episode of major depression of at least eight weeks' duration	N=275 8 weeks	Primary: HAM-D Secondary: CGI, autonomous functioning checklist, adverse events	Primary: There was no statistical significance (considered at P<0.05) or clinical significance shown for any of the prespecified primary or secondary efficacy variables in either the observed case or last observation carried forward datasets. HAM-D scores decreased by 10.7 (95% CI, 9.1 to 12.3), 9.0 (95% CI, 7.4 to 10.5), and 9.1 (95% CI, 7.5 to 10.7) points (least squares mean) for the paroxetine, imipramine, and placebo groups, respectively. Secondary: There were clinically significant increases in harms, including suicidal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				ideation and behavior and other serious adverse events in the paroxetine group and cardiovascular problems in the imipramine group.
Le Noury et al.[87] (2016) Study 329 Imipramine (200 to 300 mg/day) vs paroxetine (20 to 40 mg/day) vs placebo	Reanalysis of DB, MC, PC, RCT Adolescents 12 to 18 years of age who met DSM-IV criteria for a current episode of major depression of at least eight weeks' duration	N=119 6-month continuation phase of patients who had responded to treatment	Primary: Percentage of patients who relapsed Secondary: Safety	Primary: Relapse was not a primary endpoint of the original trial, and cannot be analyzed in a way that would allow a definitive statement about rates of relapse compared to placebo. Of patients entering the continuation phase, 15 of 49 for paroxetine (31%), 12 of 39 for imipramine (31%) and 12 of 31 for placebo (39%) completed as responders. Across the study, 25 patients on paroxetine relapsed (41% of those showing an initial response), 15 on imipramine (26%), and 10 on placebo (21%). Secondary: In the continuation and taper phases combined there were 211 adverse events in the paroxetine group, 147 on imipramine and 100 on placebo. The taper phase had a higher proportion of severe adverse events per week of exposure than the acute phase, with the continuation phase having the fewest events.
Asnis et al.[88] (2013) Levomilnacipran 40 mg QD or levomilnacipran 80 mg QD or levomilnacipran 120 mg QD vs	DB, MC, PC, RCT Patents 18 to 65 years of age, met the diagnostic criteria of MDD per the DSM-IV-TR, current ongoing depressive episode ≥8 weeks in duration, MADRS score ≥30 at baseline, MADRS-SR ≥26 at baseline	N=708 N=506 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo) Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight, mean change from baseline of	Primary: The LSMD from placebo of MADRS scores for levomilnacipran 40, 80 and 120 mg at week eight were -3.23; P=0.0186, -3.99; P=0.0038 and -4.86; P=0.0005, respectively. Secondary: The LSMD from placebo on the SDS total score for levomilnacipran 40, 80 and 120 mg was -1.4; P>0.05, -2.51; P<0.05, -2.57; P<0.05, respectively. The LSMD from placebo on the $HDRS_{17}$ for levomilnacipran 40, 80 and 120 mg was -1.2; P>0.05; -2.09; P<0.05 and -2.34; P<0.05, respectively. The LSMD from placebo on the CGI-S for levomilnacipran 40, 80 and 120 mg was -.04; P>0.05, -0.43; P<0.01 and -0.35; P<0.05, respectively. The LSMD from placebo on the CGI-I score for levomilnacipran 40, 80 and 120 mg was -0.1; P>0.05, -0.34; P<0.05 and -0.32; P<0.05, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			CGI-S total score at week eight and mean reduction from baseline of CGI-I total score at week eight (all reported as LSMD from placebo)	
Bakish et al.[89] (2013) Levomilnacipran 40 mg QD or levomilnacipran 80 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age, met diagnostic criteria per the DSM-IV-TR for recurrent MDD, current ongoing depressive episode 6 weeks to 12 months in duration, 5 or fewer major depressive episodes within the previous 5 years, MADRS score ≥26 at baseline, CGI-S score ≥4 at baseline	N=557 N=441 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo) Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight and mean reduction from baseline of CGI-S total score at week eight (all reported as LSMD from placebo)	Primary: The LSMD from placebo week eight for levomilnacipran 40 and 80 mg was -3.3; P=0.003 and -3.1; P=0.004, respectively. Secondary: The LSMD from placebo at week eight for levomilnacipran 40 and 80 mg was -1.8; P=0.046 and - 2.7; P=0.003, respectively. The LSMD from placebo on $HDRS_{17}$ scores for levomilnacipran 40 and 80 mg were -2.2; P=0.007 and -1.6; P=0.043. The LSMD from placebo on CGI-S scores for levomilnacipran 40 and 80 mg was -0.3 for both arms with P=0.020 and P=0.015, respectively.
Sambunaris et al.[90] (2013) Levomilnacipran 40 to 120 mg	DB, FD, MC, PC, RCT Patients 18 to 80 years of age, met the diagnostic	N=429 N=335 completed study	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD	Primary: The LSMD from placebo on the MADRS score at week eight was -3.095; P=0.0051 for levomilnacipran 40 to 120 mg. Secondary: The LSMD from placebo on the SDS at week eight was -2.632; P=0.0010

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	criteria for MDD per the DSM-IV-TR, ongoing major depressive episode of at least 4 weeks in duration, MADRS score ≥30 at baseline and MADRS-SR ≥26 at baseline	8 weeks	from placebo Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight, mean change from baseline of CGI-I total score at week eight, mean reduction from baseline of CGI-S total score at week eight and mean change from baseline on MEI-SF total score at week eight (all reported as LSMD from placebo)	for levomilnacipran 40 to 120 mg. The LSMD from placebo on the $HDRS_{17}$ score for levomilnacipran 40 to 120 mg was -2.146; P=0.0038. Levomilnacipran 40 to 120 mg did not show statistically significant results for the LSMD from placebo on the CGI-I total score at week eight (-0.207; P=0.0881). Levomilnacipran 40 to 120 mg showed a LSMD from placebo on the CGI-S at week eight of -0.352; P=0.0083. The LSMD from placebo on the MEI-SF for levomilnacipran 40 to 120 mg at week eight was 5.048; P=0.0382.
Montgomery et al.[91] (2013) Levomilnacipran 75 or 100 mg QD Levomilnacipran dose was increased to 100 mg/day over 12 days. vs	DB, FD, MC, PC, RCT Outpatients 18 to 70 years of age who met DSM-IV criteria for MDD (duration > 1 month) with a HDRS17 score > 22 and SDS score > 10	N=553 10 weeks	Primary: MADRS score change from baseline to week 10 Secondary: HDRS17, SDS, CGI-I, MADRS response (>50% decrease from baseline) and remission (score	Primary: Levomilnacipran was significantly “superior” to placebo on MADRS total score change from baseline to week 10 (LSMD, -4.2; 95% CI, -5.7 to -2.6; P<.0001). Secondary: Statistical significance in favor of levomilnacipran was demonstrated on change from baseline to week 10 in HDRS17 total score (LSMD, -3.4; 95% CI, -4.7 to -2.2; P<0.0001) and SDS total score (LSMD, -3.4; 95% CI, -4.6 to -2.2; P<0.0001) and subscales. Significantly more levomilnacipran patients vs placebo patients achieved MADRS response (59.1 vs 42.2%; P<0.0001) and remission (46.4 vs 26.0%; P<0.0001). Levomilnacipran was generally safe and well tolerated; more

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			<10), safety	levomilnacipran patients (9.4%) vs placebo patients (6.5%) discontinued due to adverse events, but more placebo patients vs levomilnacipran patients discontinued overall (24.9 vs 20.2%).
Montgomery et al.[92] (2015) Levomilnacipran ER 40 to 120 mg/day vs placebo	MA (5 studies) Patients 18 to 80 years of age with MDD	N=2598 8 or 10 weeks	Primary: MADRS total score, treatment response (≥50% improvement in MADRS), remission (MADRS score ≤10) Secondary: Not reported	Primary: Significantly greater improvements from baseline in MADRS total score were seen with levomilnacipran ER compared with placebo in four of five studies. The LSMDs between levomilnacipran ER and placebo were statistically significant in two fixed-dose studies (range, –3.1 to –4.9; P<0.05) and two flexible-dose studies (range, –3.1 to –4.2; P<0.05). In one flexible-dose study, the LSMD from placebo did not reach statistical significance (–1.5; P=0.25). The percentage of patients meeting the MADRS criterion for treatment response was higher with levomilnacipran ER than with placebo. In the overall population, the difference between levomilnacipran ER and placebo response rates was 10.2% (P<0.001). The difference between levomilnacipran ER and placebo in remission rates was 6.2% (P<0.05) in the overall population. Secondary: Not reported
Kornstein et al.[93] (2016) Levomilnacipran ER (40 to 120 mg/ day) vs placebo	Post-hoc analysis of 5 DB, MC, PC, RCTs Patients ≥18 years of age, with a DSM-IV diagnosis of MDD who were in a current major depressive episode; three subgroups were identified, (1) first-episode MDD, defined as all patients (treatment-naïve and	N=2,598 8 or 10 weeks	Primary: MADRS, HAM-D, SDS scores Secondary: Not reported	Primary: LSMDs between groups indicated significantly greater improvements with levomilnacipran ER versus placebo in MADRS (first-episode, -2.5; highly recurrent, -3.0; chronic, -4.9; all P<0.05) and HAM-D (first-episode, -2.1; highly recurrent, -1.6; chronic, -2.6; all P<0.05) total scores. LSMDs for SDS total score were statistically significant in the first-episode and highly recurrent MDD subgroups (both subgroups, -2.3; P<0.01). MADRS response rate was significantly higher with levomilnacipran ER versus placebo in all three subgroups (first-episode, 44.5% versus 35.0%; highly recurrent, 44.3% versus 33.5%; 36.8% versus 22.0%; all P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	previously treated) who entered the study during their first major depressive episode; (2) highly recurrent MDD, defined as all patients with ≥3 lifetime depressive episodes; and (3) chronic MDD, defined as all patients with a current episode duration ≥2 years			
Kessler et al.[94] (2018) MIR study Mirtazapine 15 to 30 mg/day vs placebo Given in combination with SSRI or SNRI	MC, PC, PG, RCT Patients 18 years of age or more, had used an SSRI or SNRI antidepressant at an adequate dose for at least six weeks, were adherent to treatment, had a BDI II score of 14 or more and fulfilled the ICD-10 criteria for depression	N=480 Up to 50 weeks	Primary: BDI II score at 12 weeks Secondary: Response, remission, measure of depression using PHQ-9, anxiety symptoms, social and physical functioning, adherence and adverse events	Primary: At 12 weeks, the mean BDI II score in those randomized to the usual care and mirtazapine group was 18.0 (SD=12.3) compared with 19.7 (12.4) in those randomized to usual care and placebo. A small difference in favor of the mirtazapine arm was found after adjustment for baseline BDI II score. There was not a statistically significant difference between the two groups in BDI II score at 12 weeks (adjusted difference in means -1.83, 95% CI, -3.92 to 0.27; P=0.09). Secondary: The adjusted OR (95% CI) between mirtazapine and placebo for response was 1.39 (0.94 to 2.07; P=0.10) and for remission was 1.29 (0.82 to 2.02; P=0.27). The adjusted difference in means (95% CI) between mirtazapine and placebo for GAD-7 was -0.98 (-1.93 to -0.03; P=0.04), PHQ-9 was -1.05 (-2.14 to 0.04; P=0.06), SF-12 (physical) was −1.09 (-2.75 to 0.57; P=0.20) and SF-12 (mental) was 3.91 (1.63 to 6.20; P=0.001). The between group differences in the secondary outcome scores at 12 weeks were in favor of the mirtazapine group. However, the differences were small, and in almost every case (apart from the GAD-7 and the mental health component of the SF-12) the CI for the difference included the null.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adherence to the trial drug was substantially lower in the mirtazapine group compared with placebo group with an adjusted OR (95% CI) of 0.55 (0.34 to 0.89; P=0.01). No between group difference was found for adverse effects using the antidepressant side effect checklist at 12 weeks.
Versiani et al.[95] (2005) Mirtazapine 15 to 60 mg daily vs fluoxetine 20 to 40 mg daily	DB, RCT Patients 18 to 65 years of age with MDD	N=297 8 weeks	Primary: Change from baseline in HAM-D_{17} score Secondary: MADRS, CGI	Primary: No statistically significant differences were noted between the two groups in change from baseline HAM-D_{17} score at any time point. Secondary: Mirtazapine treatment was associated with greater change in MADRS score at day 14 (–10.9 vs –8.5; P=0.006) and the proportion of patients with ≥50% decrease in MADRS score (21.4 vs 10.9%; P=0.031). On the CGI, the proportion of "much/very much improved" patients tended to be greater with mirtazapine (significant at day seven; 9.7 vs 3.4%, P=0.032). No significant between-group differences were observed for the majority of QOL measures. Mirtazapine produced significantly better improvements on "sleeping assessment 1" (14.9±5.2 vs 13.7±5.4; P=0.028) and "sleeping assessment 2" (P=0.013) than fluoxetine. Both agents were generally well tolerated but mirtazapine-treated patients experienced a mean weight gain of 0.8±2.7 kg compared to a mean decrease in weight of 0.4±2.1 kg for fluoxetine-treated patients (P<0.001).
Wheatley et al.[96] (1998) Mirtazapine 15 to 60 mg/day vs	DB, MC, RCT Patients with MDD 18 to 75 years of age	N=123 6 weeks	Primary: HAM-D Secondary; Not reported	Primary: The mean HAM-D_{17} scores were not different at week six for the two groups; although at week three (the estimated treatment difference was -3.4 in favor of mirtazapine; 95% CI, –6.1 to –0.76; P=0.006) and week four (the estimated treatment difference was -3.8 in favor of mirtazapine: 95% CI, –6.61 to –1.02; P=0.009), statistical significance was reported for mirtazapine.

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fluoxetine 20 to 40 mg/day				No other assessment endpoints were statistically different between the two groups at week six.
Blier et al.[97] (2009) Mirtazapine 30 mg at bedtime (may be increased to 45 mg after 4 weeks) vs paroxetine 20 mg in the morning (may be increased to 30 mg after 4 weeks) vs mirtazapine 30 mg/day plus paroxetine 20 mg/day for 6 weeks After 6 weeks, non-responders on monotherapy had the second trial drug added to their current regimen. Non-responders on combination therapy had the	DB, RCT Patients with MDD	N=61 8 weeks	Primary: MADRS, HAM-D_{17}, CGI Secondary; Not reported	Primary: There was a greater improvement on the MADRS at day 28 with combination therapy (P=0.045) when compared to monotherapy (mirtazapine; P=0.046, paroxetine; P=0.02). There was a greater improvement on the MADRS at days 35 (P=0.006) and 42 (P=0.002) with combination therapy compared to monotherapy (mirtazapine; P=0.003 and 0.001, respectively; paroxetine; P=0.011 and 0.003, respectively). Statistical significance was achieved on the HAM-D_{17} in the combination group at day 35 (P=0.02) when compared to mirtazapine (P=0.005), and at day 42 (P=0.007) when compared to both drugs alone (mirtazapine; P=0.002, paroxetine; P=0.04). Statistical significance was achieved on the CGI in the combination group at day 35 vs mirtazapine (P=0.004) and for both drugs at day 42 (mirtazapine; P=0.002, paroxetine; P=0.04). Four patients remitted by day 42 in the mirtazapine group (19%) and 5 in the paroxetine group (26%) compared to 9 patients remitted in the combination group (43%; P>0.05). At day 42, 10 patients in each of the monotherapy arms received the other drug in combination. The mean scores improved rapidly in both groups with seven and five patients achieving remission in the subsequent two weeks in the mirtazapine and paroxetine groups, respectively. Five patients on the combination had their regimens increased to 45 mg/day of mirtazapine and paroxetine 30 mg/day. Two of these patients achieved remission by day 56. Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dosage of both drugs increased by 50%.				
Behke et al.[98] (2003) Mirtazapine orally disintegrating tablets 30 to 45 mg/day vs sertraline 50 to 150 mg/day	DB, RCT Patients with MDD	N=345 8 weeks	Primary: HAM-D Secondary: CSFQ	Primary: Mirtazapine was significantly (P<0.05) more effective than sertraline at all assessments during the first two weeks of the study. After this time, HAM-D total scores were similar in both groups. Secondary: The CSFQ revealed a greater improvement in sexual functioning with mirtazapine than with sertraline at all assessments in both females and males. The differences were not statistically significant.
Guelfi et al.[99] (2001) Mirtazapine 15 to 60 mg/day vs venlafaxine 75 to 375 mg/day	DB, MC, RCT Hospitalized patients with severe depressive episode with melancholic features	N=157 8 weeks	Primary: HAM-D, MADRS Secondary: Adverse effects	Primary: A significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points (P≤0.03). Secondary: A significantly higher percentage of patients treated with venlafaxine (15.3%) than mirtazapine (5.1%) dropped out because of adverse events (P=0.037).
Feighner et al.[100] (1998) Nefazodone 200 mg BID vs placebo	DB, PC, PG Patients that were hospitalized due to depression	N=120 6 weeks	Primary: HAM-D_{17}, CGI-I, MADRS Secondary: Not reported	Primary: Nefazodone treatment resulted in a significant reduction (P<0.01) of the HAM-D_{17} total score compared to placebo from the end of the first treatment week through the end of the study (–12.2 nefazodone vs –7.7 placebo). At the end of the trial, significantly more nefazodone-treated patients (50%) than placebo-treated patients (29%) had responded, as indicated by their CGI-I score (P=0.021) or by a ≥50% reduction in their HAM-D_{17} scores (P=0.017). Significantly more patients treated with nefazodone (36%) than placebo-treated patients (14%) had a HAM-D_{17} score ≤10 at the end of treatment (P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significant treatment differences (P<0.01) in favor of nefazodone were also seen in the MADRS; the HAM-D retardation, anxiety, and sleep disturbance factors; and HAM-D item 1 (depressed mood). Patients with dysthymia in addition to major depression also showed significant improvement (P<0.05) when treated with nefazodone, with significant differences in response rates seen as early as week two and through the end of the trial. Secondary: Not reported
Dunner et al.[101] (2005) Paroxetine CR 12.5 to 62.5 mg vs placebo	DB, PC, RCT (Pooled analysis) Adults with MDD	N=303 (4 trials) 8 to 12 weeks	Primary: Changes in depressive symptoms according to HAM-D_{17} and CGI-I, patients achieving remission Secondary; Not reported	Primary: Statistically significant improvements in depressive symptoms in favor of paroxetine CR compared to placebo were observed in patients with both severe MDD (HAM-D treatment difference, –4.37; 95% CI, –6.31 to –2.42; P<0.001) and nonsevere MDD (HAM-D_{17} treatment difference, -1.89; 95% CI, –2.91 to –0.87; P<0.001). The odds of CGI-Improvement response were also significantly higher for patients receiving paroxetine CR than those receiving placebo, regardless of baseline depressive symptomatology (severe MDD: OR, 2.42; 95% CI, 1.50 to 3.91; P<0.001, nonsevere MDD: OR, 1.63; 95% CI, 1.21 to 2.19; P<0.002).
Birkenhager et al.[102] (2004) Phenelzine 10 mg BID vs tranylcypromine 10 mg BID	DB, RCT Patients 18 to 65 years of age with depression	N=77 5 weeks	Primary: HAM-D Secondary: Side effects	Primary: Seventeen patients (44%) responded to tranylcypromine and 18 patients (47%) responded to phenelzine (≥50% reduction in HAM-D; P=0.82). The mean reduction in HAM-D score was 10.4 for the tranylcypromine group vs 8.3 for the phenelzine group (P=0.23). No significant differences in response rates were demonstrated between the treatment groups (P=0.97). Secondary: A substantial number of patients experienced severe side effects, mainly dizziness, agitation, and insomnia. The incidence was the same in both samples (21%).
Hedayati et al.[103]	DB, PC, RCT	N=201	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2017) CAST Sertraline 50 to 200 mg/day vs placebo	Patients with MDD and stage 3, 4, or 5 non-dialysis-dependent chronic kidney disease	12 weeks	Improvement in QIDS-C16 (score range, 0 to 27; minimal clinically important difference, 2 points) Secondary: Improvement in QOL; adverse events	The mean change from baseline to study exit in the QIDS-C16 score was −4.1 in the sertraline group and −4.2 in the placebo group (between-group difference, 0.1; 95% CI, −1.1 to 1.3; P=0.82). Secondary: There was no significant between-group difference in change in patient-reported overall health on the Kidney Disease Quality of Life Survey (median score, 0 in the sertraline group vs 0 in the placebo group; between-group difference, 0; 95% CI, -10.0 to 0; P=0.61). Nausea or vomiting occurred more frequently in the sertraline vs placebo group (22.7 vs 10.4%, respectively; between-group difference, 12.3%; 95% CI, 1.9 to 22.6%; P=0.03), as well as diarrhea (13.4 vs 3.1%; between-group difference, 10.3%; 95% CI, 2.7 to 17.9%; P=0.02).
Lewis et al.[104] (2019) PANDA study Sertraline 50 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 74 years of age who had depressive symptoms of any severity or duration in the past 2 years, where there was clinical uncertainty about the benefit of an antidepressant	N=653 Up to 11 weeks	Primary: Depressive symptoms at 6 weeks, measured by PHQ-9 scores Secondary: Depressive symptoms and remission, generalized anxiety symptoms and mental and physical health related quality of life	Primary: Mean PHQ-9 scores at 6 weeks were 7.98 (SD=5.63) in patients allocated to sertraline and 8.76 (SD=5.86) in patients allocated to placebo. After adjustment for baseline scores and stratification variables, the adjusted proportional difference between sertraline and placebo was 0.95 (95% CI, 0.85 to 1.07; P=0.41). Secondary: The adjusted proportional difference in PHQ-9 scores across all timepoints was 0.93 (95% CI, 0.86 to 1.01, P=0.11). At 12 weeks, PHQ-9 scores were 13% lower (0.87; 95% CI, 0.79 to 0.97) in the sertraline group. At 6 weeks, GAD-7 scores were 21% lower (adjusted proportional difference=0.79; 95% CI, 0.70 to 0.89) in those allocated to sertraline than in those allocated to placebo. Mental health-related quality of life scores were higher (2.41; 95% CI, 1.14 to 3.96; P=0.00021) in the sertraline group than in the placebo group. There was no evidence observed of a difference in physical health-related quality of life.
Mowla et al.[105] (2016) Sertraline (range	DB, RCT Patients diagnosed according to DSM-	N=63 6 weeks	Primary: HAM-D Secondary:	Primary: The HAM-D total scores for the both groups were reduced at the end of the trial period without any significant difference (P=0.463). The response rates in both groups were around 60%. Depressed mood, anhedonia,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50 to 200 mg/day) vs duloxetine (range 40 to 60 mg/day)	V criteria for MDD by a board-certified psychiatrist		Not reported	suicidality, insomnia (early, middle and late), work and activity and loss of appetite improved in both groups without significant difference. Psychomotor retardation, general somatic symptoms and sexual problems improved more in the duloxetine group. Agitation, anxiety symptoms and hypochondriasis ameliorated better in the sertraline group. Secondary: Not reported
Rossini et al.[106] (2005) Sertraline 150 mg daily vs fluvoxamine 200 mg daily	DB, RCT Patients >59 years of age with MDD	N=88 7 weeks	Primary: Response rate (HAM-D) Secondary; Not reported	Primary: Response rates were 55.6% for sertraline and 71.8% for fluvoxamine. No significant difference in final response rates were observed between treatment groups (P=0.12). Secondary; Not reported
Sheehan et al.[107] (2009) Trazodone ER 150 to 375 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with MDD, current episode of MDD for a minimum of 1 month, dysphoria for most days over the previous 4 weeks, and a MADRS total score ≥26 at screening and baseline	N=412 8 weeks	Primary: Change from baseline in HAM-D-17 total score Secondary: HAM-D-17 responders, HAM-D-17 remitters, change in HAM-D-17 depressed mood item from baseline, change in MADRS total score from baseline, CGI-I responders, PGI-I responders, change in CGI-S from baseline, CGI-I at	Primary: The change in the HAM-D-17 total score from baseline decreased by an average of 11.4±8.2 and 9.3±7.9 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.012). Results demonstrated a significantly greater improvement in the mean HAM-D-17 total score in the trazodone group compared to the placebo group by the first week of treatment (day seven of titration: 5.6±5.2 vs 3.9±4.8, respectively; P=0.005). The significantly greater differences were maintained throughout the study. Secondary: The number of HAM-D-17 responders (decrease ≥50% from baseline HAM-D-17 total score) in the trazodone group was significantly greater compared to the placebo group (54.0 vs 41.2%; P=0.003). No difference in the proportion of HAM-D-17 remitters (HAM-D-17 total score ≤7) was observed between treatment groups (35.6 vs 31.9%; P=0.22).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			last study visit, PGI-I at last study visit, discontinuations due to lack of efficacy, and overall quality of sleep	The change in the HAM-D-17 depressed mood item from baseline decreased by average of 1.6±1.3 and 1.3±1.2 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.030). The change in MADRS total score from baseline also statistically favored treatment with trazodone (-16.6±11.3 vs -14.1±11.9; P=0.036). No difference in the proportion of CGI-I responders ("much improved" or "very much improved" at last study visit) was observed between treatment groups (53.3 vs 48.6%; P=0.22). No difference in the proportion of PGI-I responders ("much improved" or "very much improved" at last study visit) was observed between treatment groups (51.1 vs 43.7%; P=0.15). The change in the CGI-S from baseline decreased by 1.7±1.4 and 1.4±1.4 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.036). The CGI-I scores at the last study visit were comparable in both treatment groups (P=0.22). The PGI-I scores at the last study visit were comparable in both treatment groups (P=0.084). Four percent of patients in the trazodone group discontinued treatment due to lack of efficacy compared to 4.4% of patients in the placebo group (P>0.99). At the end of the study, patients treated with trazodone had statistically significant improvements compared to placebo in all quality of sleep parameters.
Lenox-Smith et al.[108] (2008)	DB, MC, RCT Patients 18 to 65 years of age with	N=406 12 weeks	Primary: HAM-D_{21} total score	Primary: There was no significant difference between venlafaxine ER and citalopram on the HAM-D_{21} total score (-17.0 vs -16.5, respectively; P=0.4778).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Venlafaxine ER 75 to 300 mg/day vs citalopram 20 to 60 mg/day	MDD who had not experienced a treatment response to 8 weeks of monotherapy with an adequate regimen of an SSRI		Secondary: MADRS, CGI-S, CGI-I	Secondary: There were no significant differences between venlafaxine ER and citalopram on the MADRS total scores (P=0.5002) or CGI-S (P=0.3014), or in the analyses of response (P=0.953). Significant differences between treatment groups were observed for one subscale analysis: more venlafaxine ER patients had a CGI-I score of 1 at week 12 (P=0.024).
Bielski et al.[109] (2004) Venlafaxine ER 225 mg/day vs escitalopram 20 mg/day	DB, RCT Patients with MDD	N=195 8 weeks	Primary: MADRS Secondary: Adverse effects	Primary: There were no significant differences in efficacy, remission rates, or response rates between venlafaxine ER and escitalopram. Mean changes from baseline to endpoint in MADRS total score for escitalopram and venlafaxine ER were –15.9 and –13.6, respectively. Remission (MADRS score of ≤10) rates at endpoint were 41.2% for escitalopram and 36.7% for venlafaxine ER. Response (≥50% reduction from baseline MADRS score) rates for the escitalopram and venlafaxine ER groups were 58.8 and 48.0%, respectively. Secondary: More patients in venlafaxine ER group had treatment-emergent adverse effects compared to escitalopram (85.0 vs 68.4%) but this was not statistically significant and may have been due to rapid titration of the venlafaxine dose. Venlafaxine ER had a higher incidence of discontinuation due to adverse events (16.0 vs 4.1%; P<0.01).
Nemeroff et al.[110] (2007) Venlafaxine 75 to 225 mg/day vs fluoxetine 20 to 60	DB, MC, PC, RCT Outpatients ≥18 years of age with MDD	N=308 6 weeks	Primary: HAM-D Secondary: Not reported	Primary: On the HAM-D, overall differences among treatment groups at week six did not reach significance (P=0.051), though the difference between the venlafaxine and placebo groups was significant (P=0.016). The differences between fluoxetine and placebo (P=0.358) and between venlafaxine and fluoxetine (P=0.130) were not significant. The difference on the HAM-D depressed mood item was significant among treatment groups at week six (P<0.001); both active treatments

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs placebo				were significantly more effective than placebo (venlafaxine; P<0.001, fluoxetine; P=0.024). The difference between the active treatments was not statistically significant (P=0.117). Secondary: Not reported
Rudolph et al.[111] (1999) Venlafaxine ER 75 to 225 mg/day vs fluoxetine 20 to 60 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD	N=301 8 weeks	Primary: HAM-D, MADRS, CGI Secondary: Not reported	Primary: The percentages of patients who achieved full remission of their depression (HAM-D total score ≤7) at the end of treatment were 37, 22, and 18% for the venlafaxine ER, fluoxetine and placebo groups, respectively. The differences in remission rates between venlafaxine ER and the other groups were significant (P<0.05). Venlafaxine ER produced a significant lower mean total score on the MADRS analysis than did fluoxetine (P=0.048). The P value for the statistical test of center by center interaction was not significant, indicating that treatment outcomes did not differ significantly between individual investigational sites. Secondary: Not reported
Benkert et al.[112] (1996) Venlafaxine 150 to 375 mg/day vs imipramine 200 mg/day	DB, PG, RCT Hospitalized patients with major depression and melancholia	N=167 6 weeks	Primary: HAM-D, MADRS Secondary: Not reported	Primary: No differences in the response rates on the HAM-D or MADRS were observed between treatments. Among patients who demonstrated a response on the HAM-D, there was a significantly faster onset of response (P=0.036) and sustained response (P=0.018) in the venlafaxine group. The median time to response on the HAM-D among responders was 14 days with venlafaxine and 21 days with imipramine. However, no differences between treatments were observed among responders on the MADRS. Secondary: Not reported
Kok et al.[113]	DB, RCT	N=81	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Venlafaxine ER 75 to 375 mg/day vs nortriptyline 25 to 200 mg/day	Inpatients ≥60 years of age with MDD	12 weeks	Remission (MADRS ≤10) Secondary: Remission on HAM-D and GDS, response rates	There was no significant difference in remission between the treatment groups as measured by a reduction in MADRS (venlafaxine, 27.5% vs nortriptyline, 36.6%; P=0.381). Secondary: There was no significant difference in remission rates between the treatment groups as measured by HAM-D and GDS (P=NS). There was no significant difference in response rates between the treatment groups as measured by MADRS, HAM-D, GDS, and CGI-I (P=NS).
Richard et al.[114] (2012) Venlafaxine ER, up to a maximum of 225 mg/day vs paroxetine, up to a maximum of 40 mg/day vs placebo	DB, PC, RCT Patients ≥30 years of age with idiopathic PD, without dementia, and depressive disorder or operationally defined subsyndromal depression	N=115 12 weeks	Primary: HAM-D-17 total score Secondary: MADRS, BDI-II, GDS, UPDRS, safety	Primary: Treatment effects relative to placebo, expressed as mean 12-week reduction in HAM-D-17 total score, were 6.2 points (97.5% CI, 2.2 to 10.3; P=0.0007) with paroxetine and 4.2 points (97.5% CI, 0.1 to 8.4; P=0.02) with venlafaxine ER. There was no difference noted between paroxetine and venlafaxine ER (P=0.28). Secondary: Significant beneficial effects of paroxetine and venlafaxine ER relative to placebo were apparent for the secondary outcomes (MADRS, BDI-II, and GDS; P≤0.01 for all comparisons). UPDRS total and motor scores improved in all three treatment groups, but there were no significant group differences in mean response. There was no evidence of treatment-associated worsening of motor function. One hundred patients reported at least one adverse event during the trial: 86, 85, and 90% with paroxetine, venlafaxine ER, and placebo. Insomnia was reported significantly less frequently with paroxetine compared to venlafaxine ER and placebo. There were three serious adverse events.
Mazeh et al.[115] (2007) Venlafaxine 75 to 300 mg/day	RCT, SB Inpatients ≥65 years of age with MDD who did not respond to two adequate	N=30 6 weeks	Primary: CGI, HAM-D, GDS Secondary: Not reported	Primary: Nine patients treated with venlafaxine (60%) and five patients treated with paroxetine (33%) remitted after eight weeks of treatment. Three patients from each group responded without achieving remission after eight weeks of treatment (20%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs paroxetine 10 to 60 mg/day	pharmacological treatments for depression during the current depressive episode			Four patients treated with venlafaxine (26.7%) and eight patients treated with paroxetine (53.3%) failed to respond. Mean score changes from baseline to endpoint for paroxetine were: HAM-D=-12.5, CGI=-2.3, and GDS=-3.2. Mean score changes from baseline to endpoint for venlafaxine were: HAM-D=-19.1, CGI=-2.3, and GDS=-6.0 in the venlafaxine group. Venlafaxine was more effective than paroxetine on CGI and HAM-D measures (P<0.0003). Secondary: Not reported
DeSilva et al.[116] (2012) Venlafaxine vs an SSRI	MA Published, randomized, DB, head-to-head trials, which compared venlafaxine and an SSRI in the treatment of MDD in adults	N=26 trials Duration varied	Primary: Remission, response, discontinuation Secondary: Not reported	Primary: MA using a random effect model showed that venlafaxine was more efficacious compared to SSRIs in achieving remission (OR, =1.13; 95% CI, 1.0 to 1.28; P=0.05) and response (OR, 1.17; 95% CI, 1.03 to 1.34; P=0.02). Subgroup analysis found that venlafaxine had a significantly better response rate than fluoxetine (OR, 1.28; 95% CI, 1.05 to 1.55; P=0.01). There were no significant differences in response or remission between venlafaxine and other individual SSRIs. There was no significant difference in all cause discontinuation between venlafaxine and SSRIs (OR, 1.10; 95% CI, 0.97 to 1.25; P=0.15). Venlafaxine had significantly higher discontinuation due to adverse events compared to SSRIs (OR, 1.41; 95% CI, 1.10 to 1.79; P=0.006). Secondary: Not reported
Reed et al.[117] (2012) Vilazodone 40 mg	2 DP, PC, RCT Patients with MDD	N=410 (RCT-1), 481 (RCT-2)	Primary: Change from baseline to end of treatment MADRS	Primary: Vilazodone-treated patients in both short-term studies showed greater improvement from baseline to end of treatment in mean MADRS scores than placebo-treated patients (LSM treatment difference, -3.2; P=0.00

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QD vs placebo		8 weeks	total score; mixed-effects repeated-measures analyses were conducted in the PC trials; effectiveness analyses in the long-term study included mean MADRS score change over time Secondary; Not reported	RCT-1 and -2.5; P=0.009 RCT-2). CGI-I mean scores at end of treatment reflected greater improvement with vilazodone compared to placebo in both studies (LSM treatment difference, -0.4; P=0.001 RCT-1 and -0.3; P=0.004 RCT-2). MADRS response rates were significantly greater among patients receiving vilazodone vs those receiving placebo (RCT-1, 40.4 vs 28.1%, respectively; P=0.007 and RCT-2, 43.7 vs 30.3%, respectively; P=0.002). The greater efficacy of vilazodone vs placebo was consistent for the majority of demographic and MDD characteristic subgroups. In the long-term study, the mean MADRS score improved from 29.9 (baseline) to 11.4 (week eight), 8.2 (week 24), and 7.1 (week 52). Secondary; Not reported
Khan et al.[118] (2011) Vilazodone 40 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with MDD (single episode or recurrent)	N=481 8 weeks	Primary: Change in MADRS total score Secondary: MADRS and HDRS-17 response, HDRS-21, HARS, CGI-S, CGI-I scores, CSFQ	Primary: Patients receiving vilazodone showed significantly greater improvements in mean MADRS scores compared to placebo (LSM treatment difference, -2.5; P=0.009). Secondary: Treatment with vilazodone resulted in significant improvements for the HDRS-17 (P=0.026), HDRS-21 (P=0.029), HARS (P=0.037) and CGI-S (P=0.004) scores. CGI-I scores at week eight showed significantly greater global improvement with vilazodone compared to placebo (P=0.004). The MADRS response rate was significantly greater among patients receiving vilazodone compared to placebo (43.7 vs 30.3%, respectively; P=0.002), as was the HDRS-17 response rate (44.2 vs 32.9%; P=0.013). Remission rates for vilazodone were not significantly different than placebo based on MADRS (27.3 vs 20.3%, respectively; P=0.066) or HDRS-17 (24.2 vs 17.7%, respectively; P=0.088). More patients receiving vilazodone (82.1%) experienced a treatment-related adverse event compared to placebo (64.4%). The most frequently reported adverse events with vilazodone compared to placebo were diarrhea (30.6 vs 10.7%), nausea (26.0 vs 5.6%) and headache (12.8 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				10.3%). Most adverse events were considered mild-to-moderate in nature. Treatment-related effects on sexual function as measured by CSFQ were small and similar among the treatment groups. Effects on weight were similar to placebo.
Rickels et al.[119] (2009) Vilazodone 40 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with MDD (single episode or recurrent)	N=410 8 weeks	Primary: Change in MADRS total score, HAM-D_{17} total score, and HAM-A total score, CGI-S and CGI-I scores Secondary: Response (≥50% decrease in total score on MADRS, and HAM-D_{17} total scores, or a score of 1 or 2 on the CGI-I)	Primary: The mean change on the MADRS total score was significantly greater with vilazodone compared to placebo (-12.9 vs -9.6, respectively; P=0.001). The difference was evident by week one (P<0.001) and on each subsequent visit (P<0.05). The mean change on the HAM-D_{17} total score was significantly greater with vilazodone compared to placebo (-10.4 vs -8.6, respectively; P=0.022). The difference was evident by week one and on each subsequent visit (P<0.05). The mean score change on the CGI-S was significantly greater with vilazodone compared to placebo (-1.4 vs -1.0, respectively; P=0.001). The mean score change on the CGI-I was significantly improved with vilazodone compared to placebo (2.6 vs 3.0, respectively; P=0.001). The mean change on the HAM-A total score was significantly greater with vilazodone compared to placebo (-6.6 vs -5.1, respectively; P=0.045). Secondary: Response rates were significantly better with vilazodone than with placebo on the MADRS (P=0.007), HAM-D_{17} (P=0.011), and CGI-I (P=0.001). Treatment-emergent adverse events with vilazodone included diarrhea, nausea and somnolence. Most of the adverse events were mild-to-moderate in severity.
Croft et al.[120] (2014) Vilazodone 40 mg/day vs	DB, MC, PC, RCT Patients 18 to 70 years of age with ongoing major depressive episode lasting eight or	N=505 8 weeks	Primary: MADRS Secondary: CGI-S, sustained response (MADRS total score ≤12 for	Primary: Statistically significant reductions that were consistent with greater symptom improvement were seen for vilazodone- versus placebo-treated patients (LSMD, –5.117; P<0.00001, effect size=0.54). Secondary: Decrease from baseline to week eight in CGI-S score was statistically

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placebo	more weeks and up to 12 months, MADRS total score ≥26		at least the last two consecutive double-blind visits)	greater for vilazodone versus placebo (LSMD, –0.622; P<0.00001, effect size =0.50). The difference in the rate of MADRS sustained response was also statistically significant in favor of vilazodone (27%) versus placebo (17%; P=0.0047).
Mathews et al.[121] (2015) Vilazodone 20 mg/day or vilazodone 40 mg/day vs citalopram 40 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with ongoing major depressive episode lasting eight or more weeks and up to 12 months, MADRS total score ≥26	N=1133 10 weeks	Primary: MADRS Secondary: CGI-S, sustained response (MADRS total score ≤12 for at least the last two consecutive double-blind visits), HAMA, adverse events	Primary: Vilazodone treatment (20 and 40 mg/day) compared with placebo was associated with significantly greater reduction in MADRS total scores from baseline to week 10. Statistical significance in favor of both vilazodone groups appeared at week two and was sustained throughout the double-blind period. MADRS mean change from baseline to week 10 was also significantly greater for citalopram versus placebo, demonstrating sensitivity of the study to detect treatment effects in the primary efficacy measure. Secondary: Both vilazodone groups relative to placebo showed significantly greater improvement from baseline in CGI-S scores. Sustained MADRS response rates were numerically higher for all active treatment groups compared with placebo, although the differences did not reach statistical significance. HAMA change from baseline improved over time but did not achieve statistical significance relative to placebo. The most commonly reported adverse events leading to discontinuation was nausea (placebo, n=1; vilazodone 20 mg/day, n=6; vilazodone 40 mg/day, n=3, citalopram, n=4). Adverse events that occurred in at least 5% of patients in either vilazodone group and at twice the rate of placebo were diarrhea, nausea, insomnia, and vomiting (40 mg/day group only).
Henigsberg et al.[122] (2012) Vortioxetine 1 mg QD or vortioxetine 5 mg	DB, MC, PC, PG, RCT Patients 18 to 75 years of age, had a current MDE per DSM-IV-TR criteria, ambulatory and a baseline MADRS total score	N=556 (N=505 completed study) 8 weeks	Primary: Change from baseline in HAMD-24 after eight weeks of treatment Secondary: Decrease from baseline on SDS,	Primary: At eight weeks, all treatment groups had a significantly greater decrease from baseline in HAMD-24 compared to placebo. Vortioxetine 1 mg had a decrease from baseline on the HAMD-24 of -14.82 (P<0.001). Vortioxetine 5 mg had a decrease from baseline of -15.42 (P<0.001), and vortioxetine 10 mg had a decrease from baseline on the HAMD-24 of -16.23 (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD or vortioxetine 10 mg QD vs placebo	≥26		CGI-I score and decrease from baseline on MADRS	None of the vortioxetine treatment groups had statistically significant decrease from baseline on the SDS as compared to placebo for (P values not reported). Vortioxetine 1, 5 and 10 mg all met the secondary endpoint of CGI-I compared to placebo; 2.37, 2.37 and 2.29 respectively (P<0.001 for all comparators). Vortioxetine 1, 5, and 10 mg all met statistical significance for the endpoint of decrease from baseline on the MADRS total score; -14.89, -15.09 and -15.65, respectively (P<0.001 for all).
Mahableshwarkar et al.[123] (2015) Vortioxetine 10 mg QD or vortioxetine 15 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age with MDD and a baseline MADRS total score >26 and CGI-S score ≥4	N=1111 8 weeks	Primary: Change from baseline in MADRS total score Secondary: MADRS response (≥50% decrease in the MADRS total score from baseline), MADRS remission (MADRS total score ≤10), CGI-S remission (CGI-S score ≤2), and CGI-I response (CGI-I score ≤2)	Primary: Differences from placebo in mean change from baseline MADRS scores were not statistically significant for the vortioxetine 10 mg or 15 mg groups. Secondary: For all five key secondary efficacy end points, the results were similar between the two vortioxetine groups, and differences from placebo did not reach statistical significance at the 0.025 level.
Jacobsen et al.[124] (2015) Vortioxetine 10 mg QD vs	DB, MC, PC, RCT Patients 18 to 75 years of age with MDD and a baseline MADRS total score >26 and CGI-S score ≥4	N=462 8 weeks	Primary: MADRS total score Secondary: Change from baseline in MADRS total	Primary: The mean difference between vortioxetine 20 mg and placebo for MADRS total score was –3.64 (SE ± 1.161; P=0.002). The difference between vortioxetine 10 mg and placebo in MADRS change from baseline did not reach significance at week eight (P=0.058). Vortioxetine 20 mg separated from placebo at week four and remained separated at weeks six and eight. The vortioxetine 10 mg dose also separated from placebo at weeks four and six but not at week eight.

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vortioxetine 20 mg QD vs placebo			score, MADRS responders, mean CGI-I score, change from baseline in MADRS total score in subjects with baseline HARS score ≥20, MADRS remission, and change from baseline in SDS total score	Secondary: MADRS response at eight weeks (≥50% decrease from baseline in MADRS total score) was achieved in 33.8, 39.2, and 28.4% of subjects in the vortioxetine 10 mg, 20 mg, and placebo groups, respectively (P=0.301 [10 mg vs placebo]; P=0.044 [20 mg vs placebo]). Since the difference did not reach the predefined level of statistical significance (0.025), the hierarchical testing strategy was stopped, and all subsequent P values (<0.05) were considered nominal and not statistically significant.
Jain et al.[125] (2013) Vortioxetine 5 mg QD vs placebo	DB, PC Patients 18 to 75 years of age with MDD and a baseline MADRS total score >30	N=600 8 weeks	Primary: Change from baseline in HAMD-24 total score at week six compared to placebo Secondary: Response and remission rates, CGI-I, HAMA, MADRS-S total score, adverse events	Primary: There were no significant differences in efficacy measures between subjects in the 5 mg vortioxetine and placebo groups at week six. Secondary: HAMD-24 total score in subjects with baseline HAMA >19 in the 5 mg vortioxetine group was improved at weeks three to six compared to the placebo group (P<0.05). The most common adverse events for the vortioxetine and placebo groups were nausea (19.1 and 9.4%), headache (17.1 and 15.1%) and diarrhoea (11.4 and 7.0%), respectively.
Nishimura et al.[126] (2018) Vortioxetine 5 mg QD vs	DB, MC, PC, RCT Patients 20 to 64 years of age with a primary diagnosis of MDD, a MADRS total score ≥ 26, a CGI-S score ≥ 4 and	N=600 8 weeks	Primary: Change from baseline in the MADRS total score at week 8 Secondary: MADRS response,	Primary: No statistically significant differences in the LS mean change from baseline in the MADRS total scores were observed at week 8 between placebo and any vortioxetine group in the overall population. Nominally significant improvements over placebo were observed for vortioxetine doses of 10 and 20 mg when the primary end-point was evaluated using the mixed model for repeated measures as the secondary analysis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vortioxetine 10 mg QD vs vortioxetine 20 mg QD vs placebo	had the current major depressive episode for ≥ 3 months at baseline		MADRS remission, CGI-I score and change from baseline in SDS total score	Secondary: Patients treated with vortioxetine 10 and 20 mg had nominally higher MADRS response rates at week 8 (LOCF) than those in the placebo group, resulting in OR of 1.837 (95% CI, 1.158 to 2.914; P =0.0098) for the 10 mg group and 1.604 (95% CI, 1.013 to 2.538; P =0.0437) for the 20 mg group. Response rates were not significantly different in patients treated with vortioxetine 5 mg and those receiving placebo. Remission rates were not significantly different between placebo and any vortioxetine group. Overall improvement and patient functioning, when assessed with the CGI-I and SDS, respectively, showed numerical improvement with vortioxetine 10 mg QD. At week 8, mean CGI-I scores and mean changes from baseline in the SDS total scores were nominally significantly greater for those treated with vortioxetine 10 mg than those receiving placebo.
Katona et al.[127] (2012) Vortioxetine 5 mg QD or duloxetine 60 mg QD vs placebo QD	AC, DB, MC, PC, PG, RCT Patients ≥65 years of age, with a primary diagnosis of MDD per DSM-IV-TR criteria and a MADRS score ≥26	N=453 (N=392 completed the study) 8 weeks	Primary: Change from baseline in HAMD-24 total score at weeks one, two, four, six, and eight. Secondary: Change in baseline from CGI-I, MADRS total score, HAMA and CGI-S at week eight. Cognitive changes from baseline assessed via the RAVLT and DSST at week	Primary: The vortioxetine treatment group did not meet the primary endpoint until week six of the study, and it was not reported when the duloxetine treatment group began to separate from placebo for the primary endpoint. The vortioxetine treatment group began to separate on the HAMD-24 scale from placebo at week six (P=0.024). At week eight, vortioxetine 5 mg had a mean change from baseline in HAMD-24 score of -13.7 (P<0.01), and duloxetine 60 mg had a mean change from baseline on the HAMD-24 of -15.8 (P<0.0001). Secondary: Vortioxetine 5 mg and duloxetine 60 mg both met all secondary endpoints at week eight. A change in CGI-I of -0.56 (P<0.001) was reported for the vortioxetine group, along with a decrease in MADRS total change of -4.29 (P<0.001), a decrease in HAMA scores of -2.35 (P<0.01) and a decrease of CGI-S of -0.60 (P<0.001). Duloxetine showed similar results for these secondary endpoints with a P<0.001 for all of these measures. The cognitive measures also showed positive results for both treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			eight	groups. Vortioxetine 5 mg showed a difference from placebo on the DSST change of 2.79 (P>0.05), and vortioxetine showed a difference from placebo in RAVLT for acquisition change of 1.14 (P<0.05) and delayed recall change of 0.47 (P<0.05). The duloxetine group did not show statistical significance for DSST change with a value of 0.77 (no P value reported). The duloxetine group did show statistical significance on the RAVLT for acquisition of change of 1.41 (P<0.01) and delayed recall change of 0.64 (P<0.01)
Mahableshwarkar et al.[128] (2013) Vortioxetine 2.5 mg QD or vortioxetine 5 mg QD vs duloxetine 60 mg QD vs placebo QD	DB, PC Adult patients with MDD	N=611 8 weeks	Primary: Change from baseline in the HAM-D24 Secondary: Responder rate, CGI-I), and remission rate; adverse events, ASEX	Primary: Both doses of vortioxetine were associated with declines in HAM-D24 total scores compared to placebo but were not statistically significant. At eight weeks, changes from baseline were [mean]: -10.50 (0.76) placebo, -12.04 (0.74) 2.5 mg vortioxetine, and -11.08 (0.74) 5 mg vortioxetine. Secondary: CGI-I and remission rate were not significantly different from placebo. Duloxetine treatment was associated with declines in HAM-D24 total score [-13.47(0.75); P=0.005] as well as significant improvements in secondary outcome measures vs placebo (P<0.05). The most common adverse events for vortioxetine were nausea, dry mouth, and headache. Rates of sexual dysfunction (ASEX) were 51.0, 37.5, 46.9, and 33.3% in the vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine, and placebo groups, respectively.
Boulenger et al.[129] (2014) Vortioxetine 15 mg QD or vortioxetine 20 mg	DB, MC, PC, RCT Patients 18 to 75 years of age with MDD, MADRS score ≥26, CGI-S ≥4	N=607 8 weeks	Primary: Change from baseline MADRS total score Secondary: MADRS responders, CGI-I, remission	Primary: Both doses of vortioxetine improved mean change from baseline in MADRS total score at week eight, with a mean treatment difference to placebo of −5.5 (vortioxetine 15 mg, standard error=1.1, P<0.0001) and −7.1 points (vortioxetine 20 mg, standard error=1.1, P<0.0001). The active reference duloxetine was also significantly superior to placebo (nominal P<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs duloxetine 60 mg QD vs placebo QD			(MADRS ≤10), SDS	Both doses of vortioxetine were statistically significantly superior to placebo in all the predefined key secondary efficacy analyses, including response and remission based on the MADRS.
Mahableshwarkar et al.[130] (2015) Vortioxetine 15 mg QD or vortioxetine 20 mg QD vs duloxetine 60 mg QD vs placebo QD	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with MDD	N=614 8 weeks	Primary: Change from baseline MADRS total score Secondary: HAMA, CGI-I, CGI-S, adverse events, ASEX	Primary: Treatment with vortioxetine 20 mg reduced the MADRS total score at week eight more than placebo (P=0.023). Vortioxetine 15 mg was not significantly different from placebo at week eight (P=0.224). Duloxetine 60 mg separated from placebo (P<0.001) on the primary endpoint, confirming assay sensitivity. Secondary: The key secondary efficacy endpoints did not separate from placebo (P>0.050) with either vortioxetine dose. Discontinuation due to adverse events occurred in 2.5% of patients in the placebo group, 9.5% in the vortioxetine 15-mg group, 9.1% in the vortioxetine 20-mg group, and 6.6% in the duloxetine 60-mg group. Treatment-emergent sexual dysfunction, suicidal ideation or behavior, and discontinuation symptoms were not significantly different between vortioxetine and placebo.
Robinson et al.[131] (2011) Vilazodone 40 mg QD	MC, OL Patients 18 to 70 years of age with MDD	N=616 52 weeks	Primary: Safety, sexual function (CSFQ), effectiveness (MADRS, CGI-S and CGI-I scales)	Primary: A total of 93.8% of patients had ≥1 treatment-emergent adverse events. The most frequent treatment-emergent adverse events were diarrhea (35.7%), nausea (31.6%), and headache (20.0%). The incidence of severe adverse events was 14.9%. The incidence of severe gastrointestinal adverse events was 3.5% and the incidence of severe headache was 1.2%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	Mean weight increase was 1.7 kg at week 52. At six months, mean weight change for patients with normal baseline weight was 1.3 kg; for overweight and obese patients, mean weight increases were 1.6 and 1.0 kg, respectively. The mean CSFQ scores at baseline were 46.9 for men and 38.7 for women; both scores indicative of sexual dysfunction. The CSFQ mean scores improved and exceeded threshold values for sexual dysfunction at week four for men and week eight for women. Adverse events pertaining to impaired sexual desire or function were decreased libido (4.2%) and anorgasmia including abnormal orgasm (2.3%). Those pertaining to males only were erectile dysfunction (4.2%) and delayed ejaculation (3.1%). There were a total of eight patients who had adverse events of either suicidal ideation or behavior. The mean MADRS scores improved from 29.9 at baseline to 11.4 at week eight (change, -18.5), 8.2 at week 24 (change, -21.7), and 7.1 at one year (change, -22.8). The mean CGI-S improved from 4.3 at baseline to 2.5 at week eight (change, -1.9) and 1.7 at one year (change, -2.6). The CGI-I mean score decreased from 3.5 at week one to 1.9 at week eight and 1.4 at one year. Secondary: Not reported
Baldwin et al.[132] (2012) Vortioxetine 2.5 mg QD or vortioxetine 5 mg QD	OL Patients with MDD	N=535 52 weeks	Primary: Safety and tolerability, MADRS Secondary: Not reported	Primary: Adverse events reported by >10% of patients were nausea, headache, and nasopharyngitis. Six patients had eight adverse events related to sexual dysfunction. There were no clinically significant safety findings with respect to mean changes of vital signs, weight, ECG parameters, or clinical laboratory values. Patients entered the ES with a mean MADRS total score of 13.5+8.7. The mean MADRS total score decreased (improved) by approximately 8 points to 5.5+6.0 at week 52. By the end of the study, the proportion of responders had increased from 63 to 94%, as had the proportion in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or vortioxetine 10 mg QD				remission (MADRS <10), increasing from 42 to 83%. Patients in remission (n=226) at the start of this study had a relapse rate (MADRS >22) of 9.7%. Secondary: Not reported
Cipriani et al.[133] (2009) New-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine)	MA (117 trials) Patients with MMD receiving acute treatment	N=25,928 6 to 12 weeks	Primary: Response (defined as the proportion of patients who had a reduction ≥50% from the baseline score on the HDRS or MADRS, or who scored much improved or very much improved on the CGI at eight weeks) and dropout rates Secondary: Not reported	Primary: *Direct Comparisons* Efficacy favored escitalopram over citalopram; citalopram over reboxetine and paroxetine; mirtazapine over fluoxetine and venlafaxine; sertraline over fluoxetine; and venlafaxine over fluoxetine and fluvoxamine. For dropouts, fluoxetine was better tolerated than reboxetine and citalopram than sertraline. *Multiple-treatments MA* Escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Reboxetine was significantly less efficacious than all the other 11 antidepressants. Duloxetine and paroxetine were less well tolerated than escitalopram and sertraline; fluvoxamine was less well tolerated than citalopram, escitalopram, and sertraline; venlafaxine was less well tolerated than escitalopram; reboxetine was less well tolerated than many other antidepressants, such as bupropion, citalopram, escitalopram, fluoxetine, and sertraline; and escitalopram and sertraline were better tolerated than duloxetine, fluvoxamine, paroxetine, and reboxetine. Mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than fluoxetine, and fluoxetine was more efficacious than reboxetine. Fluoxetine was better tolerated than reboxetine. Mirtazapine, escitalopram, venlafaxine, and sertraline were among the most efficacious treatments, and escitalopram, sertraline, bupropion, and citalopram were better tolerated than the other remaining antidepressants.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The cumulative probabilities of being among the four most efficacious treatments were: mirtazapine (24.4%), escitalopram (23.7%), venlafaxine (22.3%), sertraline (20.3%), citalopram (3.4%), milnacipran (2.7%), bupropion (2.0%), duloxetine (0.9%), fluvoxamine (0.7%), paroxetine (0.1%), fluoxetine (0.0%), and reboxetine (0.0%). The cumulative probabilities of being among the four best treatments in terms of acceptability were escitalopram (27.6%), sertraline (21.3%), bupropion (19.3%), citalopram (18.7%), milnacipran (7.1%), mirtazapine (4.4%), fluoxetine (3.4%), venlafaxine (0.9%), duloxetine (0.7%), fluvoxamine (0.4%), paroxetine (0.2%), and reboxetine (0.1%). Secondary: Not reported
Moncrieff et al.[134] (2004) Antidepressants vs placebo	MA Patients with MDD	N=751 (9 trials) Variable duration	Primary: Efficacy Secondary; Not reported	Primary: TCAs were statistically better than active placebo in the pooled analysis (0.39, 95% CI, 0.24 to 0.54). Secondary; Not reported
Walsh et al.[135] (2002) Antidepressants vs placebo	MA Adult outpatients with MDD	N=not specified (75 trials) Variable duration	Primary: HAM-D, CGI Secondary: Not reported	Primary: The mean proportion of patients in the placebo group who responded was 29.7% (range, 12.5 to 51.8). Response was determined by a reduction of at least 50% in their score on the HAM-D and/or CGI rating of markedly or moderately improved. Both the proportion of patients responding to placebo and the proportion responding to medication were significantly positively correlated with the year of publication (for placebo P<0.001; for medication P=0.02). The association between year of publication and response rate was more statistically robust for placebo than medication. Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Geddes et al.[136] (2003) Antidepressants vs placebo	MA Studies evaluating relapse prevention of depression	N=4,410 (31 trials) 6 to 36 months	Primary: Proportion of patients relapsing; withdrawal from the trial Secondary: Not reported	Primary: Continuing treatment with antidepressants reduced the odds of relapse by 70% (95% CI, 62 to 78; P<0.00001) compared to treatment discontinuation. The average rate of relapse on placebo was 41% compared to 18% on active treatment. The treatment effect seemed to persist for up to 36 months, although most trials were of 12 months duration, and so the evidence on longer-term treatment requires confirmation. Significantly more participants allocated antidepressants withdrew from the trials than did those allocated to placebo (18 vs 15%, respectively; OR, 1.30; 95% CI, 1.07 to 1.59). Secondary: Not reported
Mohamed et al.[137] (2017) VAST-D Switch to bupropion vs augment current treatment with bupropion vs augment with aripiprazole	MC, SB, RCT Veterans Health Administration patients ≥18 years of age with an MDD diagnosis and suboptimal response to a treatment course with a selective-serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, or mirtazapine	N=1,522 12 weeks (acute treatment phase), up to 36 weeks (continuation phase)	Primary: Remission during the acute treatment phase (QIDS-Clinician Rated score ≤5 at two consecutive visits) Secondary: Response (≥50% reduction in QIDS-Clinician Rated score or improvement on the CGI-I scale), relapse, and adverse effects	Primary: The primary outcome of remission occurring through week 12 was higher for the augment-aripiprazole group (28.9%) compared with the switch group (22.3%; RR, 1.30; 95% CI, 1.05 to 1.60; P=0.02) but not compared with the augment-bupropion group (26.9%; RR, 1.08; 95% CI, 0.88 to 1.31; P=0.47). Remission with the augment-bupropion group was not significantly different than the switch group (RR, 1.20; 95% CI, 0.97 to 1.50; P=0.09). Secondary: Response based on QIDS-Clinician score was significantly higher for the augment-aripiprazole group (74.3%) than for both the switch group (62.4%; RR, 1.19; 95% CI, 1.09 to 1.29; P<0.001) and the augment-bupropion group (65.6%; RR, 1.13; 95% CI, 1.04 to 1.23; P=0.003), with no significant difference between the augment-bupropion group and the switch group (RR, 1.05; 95% CI, 0.96 to 1.15; P=0.29). Response measured by CGI improvement similarly favored the augment-aripiprazole group (79%) compared with both the switch group (70%; RR, 1.14; 95% CI, 1.06 to 1.22; P<0.001) and the augment-bupropion group (74%; RR, 1.07; 95% CI, 1.00 to 1.14; P=0.07). Among the 396 patients achieving remission in the acute treatment phase,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				there were no significant differences in the secondary outcome of cumulative relapse: augment-bupropion group vs switch group (HR, 1.36; 95% CI, 0.78 to 2.39; P=0.70); augment-aripiprazole group vs switch group (HR, 1.12; 95% CI, 0.65 to 1.94; P=0.68); or augment-bupropion group vs augment-aripiprazole group (HR, 0.96; 95% CI, 0.58 to 1.59; P=0.87). Anxiety was more frequent in the two bupropion groups (24.3% in the switch group [n=124] vs 16.6% in the augment-aripiprazole group [n=84]; and 22.5% in augment-bupropion group [n=114]). Adverse effects more frequent in the augment-aripiprazole group included somnolence, akathisia, and weight gain.
Saveanu et al.[138] (2015) iSPOT-D Escitalopram vs sertraline vs venlafaxine ER Dose adjustments managed by each participant's usual treating clinician according to their usual clinical practice.	MC, PRO, RCT Patients 18 to 65 years of age with diagnosis of nonpsychotic MDD and HDRS-17 score ≥16	N=1008 8 weeks	Primary: HDRS-17 (response rate was defined as a ≥50% decrease in severity from baseline; remission by an HDRS-17 score ≤7) Secondary: Self-reported response and remission on the QIDS-SR16, for which response rate was a ≥50% decrease in severity from baseline to week 8, and remission a score ≤5, functional capacity, adverse events	Primary: Of the 71.6% of patients who completed the full eight weeks and at least one outcome measure at week eight, over 60% of participants met criteria for response, of which 45.4% were in remission. Response and remission rates did not significantly differ between the treatment arms. Secondary: By the QIDS-SR16, 53.3% of participants had responded, of which 37.6% were in remission at week eight. Most domains of function showed improvement on the order of one standard deviation, a clinically meaningful shift over the acute treatment phase. None of the score changes differed significantly between the three treatment arms. Adverse events (any medical symptom or condition occurring or worsening after the baseline visit) were reported by 44.8% of participants, 88.3% (399/452) of whom experienced events likely to be related to the antidepressants. Overall, 3.6% of participants discontinued due to intolerance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chuang et al.[139] (2014) Paroxetine (20 mg/day) vs venlafaxine (75 to 225 mg/day) vs milnacipran (100 mg/day)	OBS, OL Patients 18 to 65 years of age with diagnosis of MDD and HDRS-17 score ≥16	N=249 24 weeks	Primary: HDRS-17: response (score decreased more than 50%), remission (score ≤7 or ≤5, as stated) Secondary: Not reported	Primary: There were no significant differences between the three groups in response (P=0.72). There were no significant differences in remission rates between the three groups when the criterion for remission was an HDRS-17 score ≤5. However, Milnacipran was more efficacious than paroxetine in relieving the symptoms of MDD when the remission criterion was an HDRS-17 score ≤7, and, using LOCF analysis, paroxetine was more efficacious than venlafaxine when the remission criterion was an HDRS-17 score ≤5. Secondary: Not reported
Thase et al.[140] (1995) Phenelzine (PHZ) vs isocarboxazid (ISO) vs tranylcypromine (TRP) vs placebo	MA Patients with MDD	Review of Medline and Psychological abstracts from 1959 to 1992	Primary: Efficacy Secondary; Not reported	Primary: For outpatients using ITT samples, all three agents appear to be equally effective (PHZ=57.9%±4.0%; ISO=60.1%±7.1%; TRP=52.6%±12.4%). When compared to placebo in outpatients, ISO (41.3%±18.0%) had a larger relative advantage compared to either PHZ (29.5% ±11.1%) or TRP (22.1%±25.4%) in the doses studied. For inpatients, PHZ was somewhat more effective (22.3%±30.7%) than placebo, whereas the ISO-placebo difference was smaller (15.3%±12.6%). Secondary; Not reported
Cipriani et al.[141] (2005) Fluoxetine,	MA (132 trials) Patients with depression	N=9,311 Duration varied	Primary: Number of patients who responded to treatment (HAM-	Primary: On a dichotomous outcome fluoxetine was less effective than sertraline (PetoOR, 1.40; 95% CI, 1.11 to 1.76), mirtazapine (PetoOR, 1.64; 95% CI, 1.01 to 2.65) and venlafaxine (PetoOR, 1.40; 95% CI, 1.15 to 1.70; P

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sertraline, nortriptyline, amitriptyline, venlafaxine, imipramine, nefazodone, citalopram, desipramine, paroxetine, pramipexole, fluvoxamine, trazodone, bupropion, clomipramine, duloxetine, mirtazapine, doxepin			D, MADRS) Secondary: Tolerability	values not reported). On a continuous outcome, fluoxetine was less effective than venlafaxine (SMD random effect, 0.11; 95% CI, 0.00 to 0.23; P value not reported). Secondary: Fluoxetine was better tolerated than TCAs considered as a group (PetoOR, 0.78; 95% CI, 0.68 to 0.89), and was better tolerated in comparison with individual antidepressants, in particular than amitriptyline (PetoOR, 0.64; 95% CI, 0.47 to 0.85) and imipramine (PetoOR, 0.79; 95% CI, 0.63 to 0.99), and among newer antidepressants than pramipexole (PetoOR, 0.20; 95% CI, 0.08 to 0.47; P values not reported).
Stahl et al.[142] (1997) Mirtazapine up to 35 mg daily vs amitriptyline up to 280 mg daily vs placebo up to 7 capsules daily	MA Patients with MDD	N=580 (4 trials) 6 weeks	Primary: HAM-D, HDRS, responder rate (percentages of patients with ≥50% decrease in baseline 17-item HDRS score), remitter rate (patients with a total 17-item HDRS score ≤7), MADRS, CGI Secondary: Change from baseline in the "depressed mood" item on the HDRS scale, anxiety/	Primary: Compared to placebo, both mirtazapine and amitriptyline therapy significantly improved patient HDRS, MADRS, and CGI scores from baseline (P<0.05). Significantly greater percentages of patients responded to mirtazapine or amitriptyline therapy, assessed with the HDRS criteria, compared to placebo (P<0.05). Significantly greater percentages of patients randomized to mirtazapine or amitriptyline therapy exhibited remission compared to placebo (P<0.05). There were no statistically significant differences between mirtazapine and amitriptyline in any of the primary endpoints. Secondary: Significantly greater improvement from baseline in the "depressed mood" item was seen in the mirtazapine and amitriptyline groups compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			somatization factor, sleep disturbance factor, melancholia factor, tolerability	Significantly greater improvement from baseline in the anxiety/somatization, sleep disturbance, and melancholia factors was seen in the mirtazapine and amitriptyline groups compared to placebo (P<0.05). There were no statistically significant differences between mirtazapine and amitriptyline in the "depressed mood", anxiety, somatization, sleep disturbance, or melancholia factors on the HDRS scale. Patients on amitriptyline therapy experienced a significantly higher incidence of restlessness (14.0 vs 2.1%), vertigo (2.1 vs 0), blurred vision (6.2 vs 0.5%), dyspepsia (10.4 vs 0.5%), dry mouth (80.8 vs 34.0%), constipation (31.1 vs 18.0%), palpitations (8.8 vs 3.6%), and tachycardia (4.7 vs 0.5%) compared to patients receiving mirtazapine therapy (P<0.05). Patients on mirtazapine therapy experienced a significantly higher incidence of weight gain compared to the amitriptyline group (14.4 vs 6.7%; P<0.05). Drowsiness and sedation were more common in the active groups compared to the placebo group (P<0.05). Hypotension was more common in the amitriptyline group compared to the placebo (3.6 vs 0.5%; P<0.05). Increased appetite was more common in the mirtazapine group compared to the placebo group (3.6 vs 0; P<0.05).
Bull et al.[143] (2002) Continuation of an SSRI vs discontinuation of an SSRI	RETRO Adult patients diagnosed with a depressive disorder, taking an SSRI for at least 6 months were interviewed over the phone; prescribing	N=137,401 6 months	Primary: Patient-physician communication about therapy duration and adverse effects, therapy discontinuation or switching of medication within	Primary: While 72% of physicians reported instructing their patients on taking SSRIs for a minimum of 6 months, only 34% of patients acknowledged receiving this information from their physician and 56% reported receiving no instructions at all. Patients instructed to continue therapy for less than 6 months were 3 times more likely to discontinue therapy prematurely compared to those told to continue therapy for a longer duration (OR, 3.12; 95% CI, 1.21 to 8.07; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs switching of an SSRI	physicians were asked to complete a survey		three months of SSRI use, BDI-FS, depression symptoms Secondary; Not reported	Patients who were informed about adverse effects common with their medication were less likely to discontinue therapy than patients who did not have this discussion with their physician (OR, 0.49; 95% CI, 0.25 to 0.95). Patients who discussed adverse effects with their physicians were more likely to switch medications (RR, 5.60; 95% CI, 2.31 to 13.60). Patients experiencing adverse effects were 3 times more likely to switch their medication (OR, 3.09; 95% CI, 1.30 to 7.31). Less than three follow-up visits, and lack of therapeutic response to medication at three months were also associated with a higher incidence of therapy discontinuation (P=0.002, P<0.001, respectively). Patients who continued to have severe symptoms, based on the BDI-FS scale, were six times more likely to switch their medication (OR, 6.15; 95% CI, 2.11 to 17.89). Secondary; Not reported
Anderson et al.[144] (2000) TCAs vs SSRIs	MA Patients with MDD	N=10,706 (102 trials) Variable duration	Primary: HAM-D, MADRS Secondary: Adverse events	Primary: Efficacy was based on 102 studies (5,533 SSRI patients and 5,173 TCA patients). Efficacy was determined by comparing the mean reduction in depression scores based upon the HAM-D or the MADRS. There was no statistical difference in efficacy between the two groups (effect size, –0.03; 95% CI, –0.09 to 0.03). TCAs did appear more effective for inpatients (–0.23; 95% CI, –0.4 to -0.05). Secondary: SSRIs were better tolerated with discontinuations due to adverse effects significantly greater in the TCA group (12.4 vs 17.3%; P<0.0001).
MacGillivray et al.[145] (2003)	MA Patients with MDD	N=2,951 (11 trials) Variable	Primary: HAM-D; MADRS Secondary:	Primary: Efficacy between SSRI and tricyclics did not differ significantly (standardized weighted mean difference, fixed effects 0.07; 95% CI, –0.02 to 0.15; P<0.11).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TCAs vs SSRIs		duration	Tolerability	 Secondary: Significantly more patients receiving a tricyclic withdrew from treatment (RR, 0.78; 95% CI, 0.68 to 0.90; P<0.0007) and withdrew specifically because of side effects (RR, 0.73; 0.60 to 0.88; P<0.001).
Steffens et al.[146] (1997) TCAs vs SSRIs	MA Patients with MDD	N=not specified (34 trials) Variable duration	Primary: HAM-D Secondary: Frequency of side effects	Primary: Overall, the response rate to treatment for patients who completed a trial was 63.2% for SSRIs and 68.2% for TCAs (P=0.038). For the ITT groups, these rates dropped to 48.0 and 48.6% (P=NS), respectively. Significantly more TCA-treated than SSRI-treated patients dropped out due to either lack of efficacy or adverse reactions (30.0 vs 24.7%; P=0.01). Secondary: Patients taking SSRIs experienced more gastrointestinal problems and sexual dysfunction, whereas treatment with TCAs produced significantly more complaints of sedation, dizziness, and anticholinergic symptoms.
Diabetic Neuropathy				
Yan et al.[147] (2010) Duloxetine 60 to 120 mg daily vs placebo	DB, PC, RCT Adult Chinese patients with diabetic peripheral neuropathic pain and BPI 24-hour average pain severity rating ≥4	N=215 12 weeks	Primary: Change from baseline to endpoint in BPI average pain score Secondary: BPI-S and BPI-I, PGI-I, CGI-S, EQ-5D, Athens Insomnia Scale	Primary: Mean change from baseline to endpoint in BPI pain score was not significantly different between treatments (-2.31±0.18 vs -2.69±0.19; P=0.124). Duloxetine-treated patients showed significantly greater pain reduction compared to placebo-treated patients at weeks one, two, and four (P=0.004, P=0.009, and P=0.006), but not at week eight (P=0.125) and 12 (P=0.107). Secondary: Duloxetine-treated patients experienced significant improvement in PGI-I (2.32±0.11 vs 2.64±0.10; P=0.028), CGI-S (-1.24±0.11 vs -0.99±0.11; P=0.036), AUC for pain relief, BPI-S pain right now (-2.72±0.26 vs -1.99±0.25; P=0.012), and BPI-I walking ability (-2.45±0.24 vs -1.82±0.23; P=0.016). Patients receiving duloxetine had numerically higher 30 and 50% response rates on BPI average pain compared to placebo-treated patients. A higher proportion of patients receiving duloxetine (62.5%) met the criteria for sustained response compared to patients receiving placebo (50.5%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				All other secondary efficacy measures, including health outcomes measures, were numerically but not significantly improved in patients receiving duloxetine compared to patients receiving placebo.
Armstrong et al.[148] (2007) Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	3 DB, MC, PC, RCT Patients with diabetic peripheral neuropathic pain	N=1,139 12 weeks	Primary: Patient-reported functional outcomes (SF-36, BPI, EQ-5D) Secondary: Not reported	Primary: Diabetic peripheral neuropathic pain patients treated with duloxetine 60 mg QD or BID had greater improvement, compared to placebo, in all SF-36 domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Within treatment group changes among the domain scores ranged from 0.9 to 23.5 points. Duloxetine 60 mg BID showed some advantage over duloxetine 60 mg QD on general health (P=0.02) and mental health (P=0.04) status. Consistent results were seen in the ITT population with the exception that the above indicated advantages of duloxetine 60 mg BID over 60 mg QD in the domains of general and mental health were not significant. Duloxetine 60 mg QD and 60 mg BID were significantly more efficacious to placebo at reducing scores in all BPI-I items thereby indicating improvements in all seven items, with similar results demonstrated for the ITT population. In the analysis of the EQ-5D, patients on duloxetine 60 mg QD (P=0.004) and 60 mg BID (P<0.001) were both significantly better compared to placebo for the trial completers. Results for the ITT analysis were consistent, thus demonstrating the superiority of duloxetine 60 mg QD and BID compared to placebo with regard to changes in all included function and QOL measures. Secondary: Not reported
Kajdasz et al.[149] (2007) Duloxetine 20 or 60 mg QD, or 60 mg BID	Post-hoc analysis of 3 DB, MC, PC, RCT Patients with diabetic peripheral	N=1,139 12 weeks	Primary: Response rate (defined as ≥30 and ≥50% reductions from baseline in weekly	Primary: NNTs based on 50% reduction for patients receiving duloxetine 60 mg QD and 60 mg BID were 5.2 (95% CI, 3.8 to 8.3) and 4.9 (95% CI, 3.6 to 7.6), respectively, based on LOCF. Similarly, NNTs of 5.3 (95% CI, 3.8 to 8.3) for 60 mg QD and 5.7 (95% CI, 4.1 to 9.7) for 60 mg BID observed based on baseline observation carried forward.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	neuropathic pain		mean of the 24-hour average pain severity scores) Secondary: NNH (based on rates of dis-continuation due to adverse events)	Secondary: The NNHs based on discontinuation due to adverse events were 17.5 (95% CI, 10.2 to 58.8) with duloxetine 60 mg QD and 8.8 (95% CI, 6.3 to 14.7) with duloxetine 60 mg BID.
Lunn et al.[150] (2009) Duloxetine vs placebo or control Only outcomes for painful peripheral neuropathy are reported.	SR (6 RCTs) Patients with painful peripheral neuropathy or chronic pain conditions	N=2,200 ≥8 weeks	Primary: Short term (≤12 weeks) improvement in pain Secondary: Long term (>12 weeks) improvement in pain, improvement in short- and long-term pain ≥30%, improvement in any validated QOL score ≥30%	Primary: Three trials in painful diabetic neuropathy reported data on the primary outcome measure of 50% improvement of pain compared to baseline at <12 weeks. Patients were treated with duloxetine 20, 60, or 120 mg/day. Combining data from all doses from the three trials together, the RR of 50% improvement with any dose was 1.63 (95% CI, 1.35 to 1.97) greater than placebo. The RR of improvement was significantly greater compared to placebo for the 60 and 120 mg/day doses, but not 20 mg/day, for which it was 1.43 (95% CI, 0.98 to 2.09). The RR of improvement with 120 mg/day (1.66; 95% CI, 1.35 to 2.04) was not significantly greater compared to 60 mg/day (1.65; 95% CI, 1.34 to 2.03). The mean improvement in pain at <12 weeks on an 11-point Likert scale was significantly greater compared to placebo with 60 (-1.04; 95% CI, -1.37 to -0.71) and 120 mg/day (-1.16; 95% CI, -1.49 to -0.83) of duloxetine. Secondary: None of the included trials of painful diabetic neuropathy included outcomes >12 weeks. Two trials included data on >30% improvement of pain at ≤12 weeks. The results were similar to those for ≥50% improvement. Relative rates of improvement were significantly greater compared to placebo with duloxetine for the 60 mg/day (1.53; 95% CI, 1.27 to 1.83), 120 mg/day (1.55; 95% CI, 1.30 to 1.86), and for both doses combined (1.54; 95% CI, 1.30 to 1.82).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Trials that included QOL information used the SF-36. In painful diabetic neuropathy, the effect of duloxetine 20 mg was not significant on any of the selected SF-36 subscores at up to 12 weeks (relevant physical, mental, and bodily pain subsections). The WMD of improvement on the physical summary component was significantly greater with 60 mg/day (2.51; 95% CI, 1.00 to 4.01) and 120 mg/day (2.80; 95% CI, 1.04 to 4.55). The WMD on the mental summary component was significantly greater only with 120 mg/day (2.23; 95% CI, 0.69 to 3.77). The WMD on the bodily pain subscale showed significantly more improvement compared to placebo with 60 mg/day (5.58; 95% CI, 1.74 to 9.42) and with 120 mg/day (8.19; 95% CI, 4.33 to 12.05). Three trials reported the PGI-C and pain at rest, and two reported the bodily pain index. The WMD for each outcome was significant and similar in magnitude for 60 and 120 mg/day. However, a clinically meaningful differences in the PGI-C is suggested as one point and hence the change associated with 60 mg/day (-0.59; 95% CI, -0.78 to -0.41) may not be clinically significant. The RR for the bodily pain index is significantly reduced by -0.97 (95% CI, -1.38 to -0.57) but this borders on a change considered clinically significant.
Kaur et al.[151] (2011) Duloxetine 20 to 60 mg QD for 6 weeks vs amitriptyline 10 to 50 mg QD at bedtime for 6 weeks	AC, DB, RCT, XO Patients 18 to 75 years of age with type 2 diabetes who had painful diabetic neuropathy for ≥1 month	N=58 14 weeks	Primary: Reduction in the median pain score from baseline Secondary: Assessment of pain by McGill Pain Questionnaire, overall improvement score, 24-point HAM-D, change in sleep pattern, and patient self-evaluation of change in PGI-C scale	Primary: There was a significant improvement in pain at six weeks with both treatments compared to their baseline values (P<0.001 for both). For duloxetine, 59% of patients showed good improvement, 22% showed moderate improvement, and 9% showed mild improvement. For amitriptyline, 55% of patients showed good improvement, 24% showed moderate improvement, and 16% showed mild improvement. Overall pain relief of >30% was observed in 64% of patients receiving duloxetine and 62% of patients receiving amitriptyline. A >50% improvement was seen in 50% of patients receiving duloxetine and 55% of patients receiving placebo. Secondary: There was no significant difference in efficacy among the treatment groups as assessed by the McGill Pain Questionnaire and Likert scale. Significant improvement in sleep and overall well-being was observed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with both drugs (P<0.001 for both). Overall, 48% of patients preferred duloxetine compared to 36% of patients who preferred amitriptyline (P=0.18). Based on pain relief and tolerability, 5, 14 and 30% of patients preferred duloxetine 20, 40, and 60 mg, respectively. A total of 5, 22, and 9% of patients preferred amitriptyline 10, 25, and 50 mg. The number of mild treatment-emergent adverse effects was higher with duloxetine compared to amitriptyline (P<0.02). The number of moderate to severe treatment emergent adverse event was higher with amitriptyline (P<0.01). Dry mouth was significantly more common with amitriptyline that duloxetine (55 vs 24%, respectively; P<0.01).
Boyle et al.[152] (abstract) (2012) Duloxetine 60 mg/day vs amitriptyline 50 mg/day vs pregabalin 300 mg/day	AC, DB, PG, RCT Patients ≥18 years of age with diabetes (type 1 or type 2) for ≥1 year and neuropathic pain of diabetic origin (≥1 of the following: dysesthesia, burning pain, cold or heat allodynia, shooting or lancinating pains and hyperalgesia affecting both lower extremities at any level below the mid-thighs) and LANSS score >12	N=83 4 weeks	Primary: BPI Secondary: SF-36, sleep, mood and daytime sleepiness	Primary: All three treatments significantly reduced pain compared to placebo. No one treatment was "superior" to the others with regard to pain. Secondary: For sleep, pregabalin improved sleep continuity (P<0.001), whereas duloxetine increased wake and reduced TST (P<0.01 and P<0.001). Despite negative effects on sleep, duloxetine enhanced central nervous system arousal and performance on sensory motor tasks. There were no significant safety findings; however, there were a significantly higher number of adverse events in the pregabalin treatment group.
Tanenberg et al.[153] (2011) Duloxetine 60 mg/day	MC, NI, OL, RCT Adult patients with type 1 or 2 with HbA_{1c} ≤12%, and	N=407 12 weeks	Primary: Reduction from baseline in the weekly mean of the daily 24-hour	Primary: The estimated mean change in the daily pain severity score at 12 weeks was -2.6 for duloxetine and -2.1 for pregabalin, representing an observed 0.49 advantage of duloxetine; therefore, NI was established.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pregabalin 300 mg/day vs duloxetine 60 mg/day and gabapentin ≥900 mg/day (existing therapy)	diabetic peripheral neuropathic pain who had been treated with gabapentin (900 mg/day) and had an inadequate response		pain diary ratings at week 12 Secondary: Worst pain and night pain ratings, Clinician Global Impression of Severity, BPI-S and BPI-I, BDI-II, PGI-I, SDS, response rate	Significant superiority vs pregabalin in the mean daily pain diary ratings was observed at weeks, two, three, and five through 11 with duloxetine and with duloxetine plus gabapentin at weeks two and eight, but between-treatment differences at the 12-week end point met NI criteria, not statistical superiority. The NI comparison between duloxetine and combination therapy on the differences between end point mean changes in daily pain diary ratings in the ITT patient population was also met. Secondary: Reduction from baseline in BPI average pain and BPI worst pain severity ratings was significantly greater with duloxetine vs pregabalin, but differences between treatments were not significant for the other BPI pain measures, CGI-S, depressive symptoms, or the SDS global measure. Also, no significant between-treatment differences were found among the various response outcomes.
Quilici et al.[154] (2009) Duloxetine vs pregabalin and gabapentin Placebo was used a common comparator.	MA (11 RCTs; duloxetine, 3 trials; pregabalin, 6 trials; gabapentin, 2 trials) Patients with diabetic peripheral neuropathic pain	N=not specified ≥5 to 13 weeks	Primary: Reduction in 24-hour pain severity, response rate (≥50% pain reduction), overall health improvement (PGI-I and PGI-C) Secondary: Not reported	Primary: Direct comparisons All three agents were more efficacious to placebo for all efficacy parameters. For 24-hour pain severity effect values were -1.13 (95% CI, -1.36 to -0.89), -0.90 (95% CI, -1.23 to -0.57), and -1.44 (95% CI, -2.21 to -0.66) with duloxetine, pregabalin, and gabapentin. Corresponding effect values for response rates were 0.86 (95% CI, 0.63 to 1.09; NNT, 5; 95% CI, 3 to 7) and 0.84 (95% CI, 0.52 to 1.16; NNT, 5; 95% CI, 4 to 8) with duloxetine and pregabalin, and for PGI-I/C were -0.76 (95% CI, -1.00 to -0.51) and -1.29 (95% CI, -1.72 to -0.86) with duloxetine and pregabalin. Indirect comparisons For the primary efficacy outcome of 24-hour reduction in pain severity, a difference of -0.248 (95% CI, -0.677 to 0.162) was observed in favor of duloxetine over pregabalin. Duloxetine was not inferior to pregabalin on this outcome. For response rates, the difference between duloxetine and pregabalin was close to zero and not significant. For PGI-I/C outcomes, pregabalin showed an improvement of 0.542 points over duloxetine, a difference that reached significant (95% CI, 0.016 to 1.060).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wernicke et al.[155] (2007) Duloxetine 60 mg BID vs routine care (gabapentin, amitriptyline, and venlafaxine)	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	N=293 52 weeks	Primary: Not reported Secondary: Health outcomes	Primary: Not reported Secondary: There were significant treatment-group differences observed in favor of duloxetine in the SF-36 physical component summary score, and subscale scores of physical functioning, bodily pain, mental health, and vitality. A significant treatment-by-investigator interaction was seen for general health perceptions (P=0.073), mental health (P=0.092), and social functions (P=0.003) subscales. There were no significant treatment-group differences observed on the EQ-5D questionnaire. During the trial, four deaths occurred. Deaths were considered to be unrelated to the study drug or protocol procedures. During the trial, 22 (11.2%) duloxetine vs 16 (16.7%) routine care-treated patients experienced at least one serious adverse event. The most frequently reported serious adverse events for both treatments together were cerebrovascular accident and diabetes, and these events were not considered to be drug-related. Fourteen (4.8%) patients discontinued due to any adverse event; which included 11 and three duloxetine- and routine care-treated patients (P=0.560). A total of 157 (53.6%) patients reported at least one treatment-emergent adverse event, and there were no treatment-group differences in the overall incidence of these events. There was a significant increase in mean uric acid levels in routine care-treated patients compared to duloxetine-treated patients with regard to chemistry/urinalysis. Both treatments experienced a slight increase in HbA_{1c}, with duloxetine-treated patients experiencing a larger increase in the mean change from baseline to endpoint (P<0.001). No significant treatment-group differences were observed in low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride levels.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant treatment-group differences observed in the mean change in the Michigan Neuropathy Screening Instrument score from baseline to endpoint. There were no significant treatment-group differences observed in either subset of patients in the ulnar F-wave, ulnar distal sensory latency, and peroneal compound muscle action potential from baseline to endpoint for all patients. There was a significant increase observed in the peroneal F-wave measure for routine care-treated patients (P=0.05). There were no significant treatment-group differences observed for any of the ophthalmologic exam measures. There was a significant treatment-group difference observed in the mean change in microalbumin/creatinine ratio from baseline to endpoint (P=0.031), with duloxetine-treated patients experiencing a bigger mean decrease compared to routine care-treated patients. There was no significant treatment-group difference observed in the mean change from baseline to endpoint vital signs and weight. One duloxetine-treated patient and one routine care-treated patient met the definition for sustained elevation in SBP, and there were no significant differences between treatments. There were no ECG parameters that were significantly different between treatments. Significantly more routine-care patients had potentially clinically significant Fridericia-corrected QT interval increases (P=0.034).
Raskin et al.[156] (2006) Duloxetine 60 mg BID vs	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2	N=237 52 weeks	Primary: Not reported Secondary: SF-36, EQ-5D	Primary: Not reported Secondary: No significant treatment-group differences were observed in the SF-36 subscales or in the EQ-5D questionnaire.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
routine care (gabapentin, amitriptyline, and venlafaxine)	diabetes			
Fibromyalgia				
Arnold et al.[157] (2012) Duloxetine 30 mg/day	DB, PC, RCT Patients meeting the criteria for primary fibromyalgia as defined by the American College of Rheumatology	N=308 12 weeks	Primary: Average pain severity item from the BPI-Modified Short Form, Secondary: PGI-I, FIQ total score and those measuring pain, depression, anxiety, health outcomes, and safety	Primary: Duloxetine-treated patients did not have a statistically significant BPI-Modified Short Form average pain severity reduction vs placebo-treated patients (-2.04 vs -1.70; P=0.202). Secondary: There was a significant difference between duloxetine-treated and placebo-treated patients (P<0.05) for the PGI-I endpoint score (2.97 vs 3.35) and the changes in FIQ total score (-14.62 vs -9.75) and the SF-36 mental component score. Discontinuations due to adverse events did not differ significantly between treatment groups; nausea and dry mouth were the only adverse events with a significantly higher incidence with duloxetine vs placebo.
Arnold et al.[158] (2009) Duloxetine 60 to 120 mg/day vs placebo	DB, MC, PC, RCT (pooled analysis of 4 trials) Outpatients ≥18 years of age with fibromyalgia and a score ≥4 on the average pain severity item of the BPI	N=1,332 12 to 15 weeks	Primary: Pain severity (BPI) Secondary: BPI pain interference items, FIQ, CGI-S, PGI-I, HAM-D, SF-36, SDS, MFI	Primary: In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved ≥30% reduction in BPI average pain score from baseline compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.34). In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved ≥50% reduction in BPI average pain score from baseline compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.39). Secondary: For both depressed and nondepressed patients, mean changes from baseline to endpoint on the FIQ, SDS, and CGI-S were significantly greater for duloxetine-treated patients compared to placebo-treated patients (P<0.05). All treatment-by-MDD status interactions were not significant for these assessments (P value not significant). In patients with MDD, significant differences in baseline to endpoint mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				changes between duloxetine-treated and placebo-treated patients were observed for the following SF-36 domains: mental component score, mental health score, bodily pain, physical role functioning, social functioning score, and vitality score. In patients without MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated patients were observed for the following SF-36 domains: mental component score, mental health score, general health score, bodily pain, physical functioning, emotional role functioning score, and vitality score. With the exception of the mental health subscale, for all SF-36 domains and composite scales, the treatment-by-MDD status interactions were not significant. In patients with MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated mental fatigue and reduced motivation; whereas in patients without MDD, the only significant difference between the duloxetine-treated and placebo-treated groups was observed for the mental fatigue score. For all MFI domains, the treatment-by-MDD status interactions were not significant. In the MDD subgroup, the mean improvement on the clinician-rated HAM-D-17 total score from baseline to endpoint was significantly greater for duloxetine-treated patients compared to placebo-treated patients. In patients without MDD, the mean improvement on the HAM-D-17 total score from baseline to endpoint was not significantly different between the treatment groups. The treatment by- MDD status interaction was not significant (P=0.14). For both depressed and nondepressed patients, significantly more duloxetine-treated patients rated themselves as ‘‘much improved’’ or ‘‘very much improved’’ compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.45).
Russell et al.[159] (2008) Duloxetine 20 mg/day	DB, MC, PC, RCT Patients ≥18 years of age with fibromyalgia	N=502 6 months	Primary: Pain severity (BPI), PGI-I Secondary: FIQ, CGI-S,	Primary: After three months of therapy, patients treated with duloxetine 60 and 120 mg/day experienced significantly greater improvements in average pain severity score compared to patients treated with placebo (-1.99, -2.31, -1.39, respectively; P≤0.05 and P≤0.001 vs placebo, respectively). There was no significant difference in pain severity with duloxetine 20 mg/day.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs duloxetine 60 mg/day vs duloxetine 120 mg/day vs placebo			tender-point pain assessments, MFI, HAM-D-17, SDS, SF-36, EQ-5D	At the six-month endpoint, patients treated with duloxetine experienced greater improvements in average pain severity score compared to patients treated with placebo (duloxetine 20/60 mg/day, -2.22 [P≤0.05]; duloxetine 60 mg/day, -1.98 [P≤0.05]; duloxetine 120 mg/day, -2.26 [P≤0.01]). After three months of therapy, the mean endpoint PGI-I score was significantly lower in patients treated with duloxetine 20 and 120 mg/day compared to patients treated with placebo (2.79, 2.93, 3.37, respectively; P≤0.01 and P≤0.05 vs placebo, respectively). There was no significant difference in PGI-I scores with duloxetine 60 mg/day compared to placebo. After six months of therapy, the mean endpoint PGI-I score was significantly lower in the duloxetine 20/60 mg/day (2.79; P≤0.01) and duloxetine 120 mg/day groups (2.93; P≤0.05), but not the duloxetine 60 mg/day group (3.08; P value not significant) compared to the placebo group (3.37). Secondary: After three months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (60 and 120 mg; P≤0.01 and P≤0.001, respectively), SF-36 mental component score (120 mg; P≤0.05), and some of the MFI domains (20, 60, 120 mg; P≤0.05, P≤0.01, and P≤0.001) compared to placebo-treated patients. There were no differences between duloxetine and placebo on other secondary efficacy and health outcome measures. After six months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (20/60 mg/day; P≤0.05, 60 mg/day; P≤0.01, 120 mg/day; P≤0.001) and MFI mental fatigue domain (20/60 mg/day; P≤0.05, 60 mg/day; P≤0.05, 120 mg/day; P≤0.01). The other efficacy and health outcome measures that achieved significance in the duloxetine treatment groups compared to the placebo group included the MFI physical fatigue domain and EQ-5D (duloxetine 20/60 mg/day) and the MFI physical fatigue, reduced motivation, and reduced activity domains, as well as SF-36 mental component score (duloxetine 120 mg/day). Response rates (defined as a ≥50% improvement from baseline to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				three-month endpoint in the average pain severity score) were significantly greater for duloxetine 120 mg/day (40.1%; P=0.003), but not for duloxetine 60 mg/day (34.0%; P=0.067) or for duloxetine 20 mg/day (32.5%; P=0.200) compared to placebo (23.7%). Response rates from baseline to the six-month endpoint were significantly greater for duloxetine 20/60 mg/day (36.4%; P=0.025), duloxetine 60 mg/day (32.6%; P=0.045), and duloxetine 120 mg/day (35.9%; P=0.009) compared to placebo (21.6%). In patients diagnosed with MDD at study entry, least squares mean changes in HAM-D-17 total score at six months were -4.8 for placebo, -5.2 for duloxetine 20/ 60 mg/day, -6.9 for duloxetine 60 mg/day, and -7.2 for 120 mg/day. Treatment group differences were not statistically significant when compared to placebo.
Mease et al.[160] (2010) Duloxetine 60 to 120 mg/day	ES Patients ≥18 years of age with fibromyalgia	N=278 6 months	Primary: Safety, efficacy Secondary: Not reported	Primary: Overall study drug compliance during the six-month ES was 81% in Study 1 and 79% in Study 2. The most common adverse events leading to discontinuation were fatigue and insomnia in Study 1, and diarrhea and nausea in Study 2. The most common treatment-emergent adverse events in Study 1 were nausea, dry mouth, and insomnia. The most common treatment-emergent adverse events in Study 2 were dry mouth, nausea, headache, hyperhidrosis, and muscle spasm. The majority of the treatment groups showed small mean change improvements in the BPI average pain severity score over the final six-month period. The placebo/duloxetine groups in both studies showed significant improvement in the PGI-I, as well as improvement in nearly all other efficacy and health outcome measures, including significant improvement in several SF-36 measures. The maintenance of efficacy analysis in Study 2 did not demonstrate statistical significance (90% CI, -0.39 to 0.77; P=0.580). The mean change in the BPI average pain severity score increased by 0.19 point during the extension phase. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gilron et al.[161] (2016) Pregabalin and duloxetine vs pregabalin vs duloxetine vs placebo Participants were allowed to continue NSAIDs, acetaminophen, and/or opioids (≤200 mg oral morphine equivalents)	DB, RCT, XO Patients 18 to 70 years of age with fibromyalgia and daily pain (≥4/10) for at least three months	N=41 6 weeks	Primary: Average pain intensity (0 to 10 scale) Secondary: Worst pain intensity over the past 24 hours and average nocturnal pain intensity during sleeping hours, global pain relief, adverse events	Primary: Average pain (mean ± SEM) was as follows: placebo, 5.1 ± 0.3; pregabalin, 5.0 ± 0.3; duloxetine, 4.1 ± 0.3; combination, 3.7 ± 0.3. Pain with combination was lower than placebo (P<0.001) and pregabalin (P<0.001). Pain with duloxetine was lower than placebo (P<0.001) and pregabalin (P=0.003). The comparison of combination to duloxetine resulted in a P-value of 0.09. Secondary: Proportions of participants reporting at least moderate global pain relief at maximum tolerated dose were 18.4% on placebo, 38.5% on pregabalin, 41.7% on duloxetine, and 67.7% on combination. The P value for the comparisons were 0.03 between combination and duloxetine; 0.02 between combination and pregabalin; <0.0001 between combination and placebo; 0.04 between duloxetine and placebo; 0.08 between pregabalin and placebo; and 0.82 between duloxetine and pregabalin. Worst pain with combination (4.5 ± 0.3) was lower than placebo (6.0 ± 0.3, P<0.0001) and pregabalin (5.9 ± 0.3, P<0.0001); worst pain with duloxetine (4.8 ± 0.3) was lower than placebo and pregabalin (P<0.0001 and P=0.0002, respectively). Nocturnal pain with combination (3.2 ± 0.4) was lower than placebo (4.4 ± 0.3, P=0.0001) and pregabalin (4.2 ± 0.4, P=0.0007) but failed to reach significance with duloxetine (3.8 ± 0.3, P=0.052); nocturnal pain with duloxetine was lower than placebo (P=0.03). At maximum tolerated dose, drowsiness was more frequent with combination (26.5%) vs duloxetine (5.3%, P=0.02) and also vs placebo (5.3%, P=0.02); insomnia was significantly more frequent with placebo (34.2%) vs combination (11.8%, P=0.03) and also vs pregabalin (7.9%, P=0.01).
Bidari et al.[162] (2019) Duloxetine 30 to 60 mg/day	OL, RCT Women 18 to 65 years of age with a diagnosis of fibromyalgia	N=99 4 weeks	Primary: Mean difference in score change for Widespread Pain Index (WPI) and BDI-II at week	Primary: WPI scores improved with a statistically significant difference between the two treatment arms, favoring duloxetine (Mean difference in score change -2.32, 95% CI, -4.46 to - 0.18; P=0.034). No significant difference was detected for BDI-II between the two treatment arms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pregabalin 75 to 150 mg/day			four Secondary: Mean difference in change of sub-scores and total score for FIQ-R and SF-12 and difference in cumulative incidence of adverse events	Secondary: No significant difference was detected for FIQ-R or SF-12 between the two treatment arms. Most adverse events occurred during the first and second week of the trial. Overall incidence of nausea was significantly higher in the duloxetine arm compared to the pregabalin arm. Although there was a higher incidence of constipation, dry mouth, headache, insomnia and hot flashes in the duloxetine arm, no statistical significance was detected. Furthermore, some patients in the duloxetine arm experienced blurred vision, decreased appetite, and generalized weakness, while the patients in the pregabalin arm did not report these adverse events. In contrast, higher incidence of dizziness, light headedness, and drowsiness was reported by patients in the pregabalin arm, with no significant difference between the two treatment arms.
Hauser et al.[163] (2013) Duloxetine or milnacipran vs placebo	MA, SR (10 RCTs) Adult patients >18 years of age with clinical diagnosis of fibromyalgia syndrome by any published, recognized and standardized criteria	N=6,038 Study duration had to be >4 weeks	Primary: Reduction in pain (50%), fatigue, sleep problems, disease-related QOL as measured by total score of FIQ, safety Secondary: 30% reduction in pain, depression, anxiety, disability, sexual function, PGI-C or CGI, cognitive disturbances, tenderness	Primary: Duloxetine and milnacipran had a small effect over placebo in reducing pain (SMD, -0.23; 95% CI, -0.29 to -0.18; 6.1% relative improvement; P<0.001). One-hundred and ninety-two participants per 1,000 on placebo reported an at least 50% pain reduction compared to 286 per 1,000 on duloxetine or milnacipran (RR, 1.49; 95% CI, 1.35 to 1.64; NNT, 11; 95% CI, 9 to 15; P<0.0001). Duloxetine and milnacipran did not reduce fatigue substantially (SMD, -0.14; 95% CI, -0.19 to -0.08; 2.5% relative improvement; NNT, 17; 95% CI, 12 to 29; P<0.001), and did not improve QOL substantially (SMD, -0.20; 95% CI, -0.25 to -0.14; 4.6% relative improvement; NNT, 12; 95% CI, 9 to 17; P<0.001) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD, -0.07; 95% CI, -0.16 to 0.03; 2.5% relative improvement; P=0.15). Secondary: Duloxetine and milnacipran had a significant effect over placebo in 30% pain reduction (RR, 1.36; 95% CI, 1.26 to 1.46; P<0.0001). Duloxetine and milnacipran did not reduce depression substantially (SMD, -0.15; 95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CI, -0.21 to -0.10; P<0.001), and did not improve disability substantially (SMD, -0.22; 95% CI, -0.28 to -0.16; P<0.001) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipran and placebo in reducing anxiety (P=0.54). Out of two studies that reported on sexual function, one study lacked data for reporting and the other study found no difference in reducing sexual problems between milnacipran and placebo. Duloxetine and milnacipran did not improve PGI-C substantially (SMD, -0.27; 95% CI, -0.33 to -0.21; P<0.001), did not have a substantial effect on cognitive disturbances (SMD, -0.15; 95% CI, -0.21 to -0.10; P<0.001), and did not substantially raise the tender point pain threshold (SMD, -0.23; 95% CI, -0.35 to -0.12; P<0.001), compared to placebo. Dropout rates due to adverse events were significantly higher in duloxetine or milnacipran groups at 20.6% compared to 10.9% in the placebo groups (RR, 1.83; 95% CI, 1.53 to 2.18; NNH, 11; 95% CI, 9 to 13; P<0.001). There was no statistically significant difference in serious adverse events between either duloxetine or milnacipran and placebo (RR, 0.78; 95% CI, 0.55 to 1.12; P=0.15). The most frequently reported symptoms leading to stopping medication were nausea, dry mouth, constipation, headache, somnolence/dizziness and insomnia.
Hauser et al.[164] (abstract) (2010) Duloxetine, milnacipran or pregabalin vs placebo	MA (17 RCTs) Patients with fibromyalgia syndrome	N=7,739 Not noted (efficacy noted up to 6 months)	Primary: Symptom reduction (pain, fatigue, sleep disturbance, depressed mood, reduced HRQoL) and adverse events Secondary: Not reported	Primary: Duloxetine, milnacipran and pregabalin were superior to placebo for the outcomes noted except for the following: duloxetine for fatigue, milnacipran for sleep disturbance, and pregabalin for depressed mood were not more efficacious to placebo. There were no significant differences between duloxetine, milnacipran, or pregabalin for 30% pain relief per adjusted indirect comparisons. Differences in average symptom reduction were noted as follows: duloxetine and pregabalin were more efficacious to milnacipran in reduction of pain and sleep disturbances; duloxetine was more efficacious to milnacipran and pregabalin in reducing depressed mood; and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				milnacipran and pregabalin were more efficacious to duloxetine in reducing fatigue. Secondary: Not reported.
Generalized Anxiety Disorder (GAD)				
Rynn et al.[165] (2008) Duloxetine 60 or 120 mg/day vs placebo	DB, PC, RCT Adult patients with GAD	N=327 10 weeks	Primary: HAMA total score Secondary: Response rate (HAMA total score reduction ≥50% from baseline), CGI-I, SDS, safety	Primary: Duloxetine resulted in significantly greater improvement in HAMA total scores compared to placebo (P=0.023); mean decrease for duloxetine was 8.12 (36% improvement from baseline) compared to a mean decrease of 5.89 (25% improvement from baseline). Significant differences between the two treatments were observed at week two of treatment and remained significant at each subsequent visit (P≤0.001). Secondary: Response and sustained improvement rates were significantly greater for duloxetine-treated patients compared to placebo-treated patients (P<0.05). With duloxetine, the response rate was 40% and sustained improvement was 43.7% compared to 32.0 and 33.1% with placebo. There was no difference in the proportion of patients meeting the criteria for remission (28 vs 23%; P=0.27). Duloxetine resulted in a significantly greater functional improvement based on CGI-I scores compared to placebo (2.68 vs 2.97; P=0.04). Duloxetine-treated patients were significantly more improved compared to placebo-treated patients on SDS global functioning (P<0.01), and work, social, and family/home improvement scores (P<0.05). The rate of discontinuation due to an adverse event was significantly higher with duloxetine compared to placebo (P=0.002). The most commonly reported adverse events with duloxetine treatment were nausea, dizziness, and somnolence.
Koponen et al.[166] (2007) Duloxetine 60 or	DB, MC, PC, PG, RCT Patients ≥18 years	N=513 9 weeks	Primary: HAMA total score Secondary:	Primary: Both doses of duloxetine demonstrated significantly greater improvements in HAMA total scores compared to placebo (P≤0.001 for both). Both doses of duloxetine resulted in mean decreases in HAMA total score that

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
120 mg/day vs placebo	of age with GAD of at least moderate severity		SDS; HAMA psychic and somatic anxiety factor scores; HAMA response, remission, and sustained improvement rates, safety	were more than four points greater than the decreases achieved with placebo; the mean change represents a 49% decrease from baseline with duloxetine. Significant differences between duloxetine and placebo were observed as early as two weeks after treatment initiation, and remained significant at each subsequent visit. Secondary: Both doses of duloxetine demonstrated significantly greater functional improvements in SDS global and specific domain scores compared to placebo (P≤0.001). Both doses of duloxetine achieved a mean decrease of more than three points greater than the decreases achieved with placebo; the mean change represents a 47% improvement from baseline with duloxetine. Both doses of duloxetine demonstrated significantly greater improvements in HAMA psychic and somatic anxiety factor scores compared to placebo (P≤0.001 for all comparisons). Both doses of duloxetine resulted in significantly greater HAMA response (58, 56, and 31% with duloxetine 60 mg/day, duloxetine 120 mg/day, and placebo; P≤0.001 for both), remission (31, 38, and 19%; P≤0.01 for duloxetine 60 mg/day vs placebo and P≤0.001 for duloxetine 120 mg/day vs placebo), and sustained improvement rates (64, 67, and 43%; P≤0.001 for both) compared to placebo. There were no significant differences between the two doses of duloxetine on any of the efficacy outcome measures. Approximately 20% of patients receiving duloxetine had their dose decreased during the first two weeks of acute treatment. The rate of study discontinuation due to an adverse event was 11.3, 15.3, and 2.3% with duloxetine 60 mg/day, duloxetine 120 mg/day, and placebo (P≤0.001). Overall, nausea was the most frequent adverse event, which resulted in study discontinuation for 6.0 and 2.4% of duloxetine 60- and 120 mg/day-treated patients.
Alaka et al.[167] (2014)	DB, MC, PC, RCT	N=291	Primary: HAMA total score	Primary: Patients treated with duloxetine versus placebo had significantly greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duloxetine 30 to 120 mg/day vs placebo	Patients ≥65 years of age with GAD with at least moderately severe symptoms	10 weeks	Secondary: SDS, adverse events	baseline-to-endpoint improvement on the HAMA total score (−15.9 vs −11.7; P<0.001). Significance between treatment group differences began as early as week four and continued to study end at week 10. Secondary: Duloxetine demonstrated a greater effect than placebo on mean changes from baseline in SDS global scores (−8.6 vs −5.4; P<0.001). Treatment-emergent adverse events occurred in ≥5% of duloxetine-treated patients and twice the rate than with placebo including constipation (9 vs 4%; P=0.06), dry mouth (7 vs 1%; P=0.02), and somnolence (6 vs 2%; P=0.14).
Davidson et al.[168] (2008) Duloxetine vs placebo All patients received OL duloxetine for 26 weeks. Treatment responders (≥50% reduction in HAMA total score to ≤11 and "much"/"very much improved" ratings for the last 2 visits of the OL phase.	DB, PC, RCT Patients ≥18 years of age with moderate to severe GAD	N=533 (N=887 OL phase) 26 weeks	Primary: Time to relapse (increase in CGI-S rating ≥2 points from randomization to a score ≥4 while meeting criteria for GAD or by discontinuation due to lack of efficacy) Secondary: HAMA total score, HAMA psychic factor score, HAMA somatic factor scores, HADS-A, CGI-I, PGI-I, SDS, EQ-5D VAS, safety	Primary: Significantly more placebo-treated patients (41.8%) met relapse criteria compared to duloxetine-treated patients (13.7%; P≤0.001). Among patients who did relapse, duloxetine-treated patients had a longer time to relapse compared to patients who were switched to placebo (P≤0.001). Secondary: Patients who continued duloxetine maintained the improvements that were demonstrated during the OL phase. Patients who were switched to placebo significantly worsened on each of the secondary outcomes, including HAMA total score, HAMA psychic factor score, HAMA somatic factor scores, and HADS-A (P≤0.001 for all comparisons). The remission rate for duloxetine-treated patients at endpoint was 68.1 and 39.3% for placebo-treated patients (P≤0.001). Patients receiving placebo were rated as overall less improved by the CGI-I and PGI-I mean endpoint scores compared to patients receiving duloxetine (P≤0.001 for both). Patients treated with placebo also had worsening of their role functioning in all SDS domains of work/school, social life, and family/home management compared to patients who continued with duloxetine (P≤0.001). By endpoint, mean SDS global functioning impairment score with placebo had significantly increased into the range indicating mild to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				moderate impairment (P≤0.001). The switch to placebo was also associated with decreased life satisfaction and poorer perceived health, as measured by changes in EQ-5D VAS scores (P≤0.001 for all comparisons) compared to patients who continued duloxetine. During the OL phase, 15 treatment-emergent adverse events occurred at a frequency of ≥5%: nausea (28.3%), headache (18.7%), dry mouth (14.3%), diarrhea (14.2%), dizziness (13.4%), constipation (12.5%), fatigue (11.5%), hyperhidrosis (10.0%), insomnia (9.8%), somnolence (8.2%), decreased appetite (6.1%), upper respiratory tract infection (5.5%), decreased libido (5.4%), vomiting (5.4%), and nasopharyngitis (5.0%). Most adverse events were mild to moderate in severity. During the DB, continuation phase patients experienced discontinuation-emergent adverse events as the study medication was being withdrawn. Compared to patients receiving duloxetine, dizziness was the only adverse event to occur significantly more often with patients receiving placebo (9.9 vs 3.7%; P≤0.05). No significant increases in pulse rate, DBP, or SBP were observed in duloxetine-treated patients compared to placebo-treated patients. Most events were mild to moderate in severity. Discontinuation from study due to adverse events occurred in four and two patients receiving duloxetine and placebo.
Hartford et al.[169] (2007) Duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs	DB, MC, PC, RCT Outpatients ≥18 years of age with GAD	N=487 10 weeks	Primary: HAMA total score Secondary: HAMA psychic anxiety factor score, somatic anxiety factor score, mood item, and tension item; HADS anxiety and depression subscales scores;	Primary: Patients receiving duloxetine or venlafaxine ER experienced greater improvements in anxiety symptom severity (as measured by HAMA) compared to patients receiving placebo (duloxetine; P=0.007 and venlafaxine ER; P<0.001). The mean decrease in the HAMA total scores was 11.8 for duloxetine and 12.4 for venlafaxine ER compared to 9.2 for placebo. Secondary: Patients treated with duloxetine and venlafaxine ER demonstrated greater improvements in HAMA psychic anxiety factor score, HAMA anxious mood, HAMA tension, and HADS anxiety and depression subscales compared to patients treated with placebo (P<0.01 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			CGI-I, PGI-I; SDS	Patients treated with both duloxetine and venlafaxine ER had greater improvement ratings at endpoint on the CGI-I and PGI-I compared to patients treated with placebo (P<0.01 for all comparisons). Treatment response was seen in 47% of patients receiving duloxetine, 54% of patients receiving venlafaxine ER, and 37% of patients receiving placebo (P<0.001 for venlafaxine ER vs placebo). Using the CGI-I endpoint score, the percentage of responders was greater for duloxetine (55.7%; P=0.007) and venlafaxine ER (60.4%; P<0.001) compared to placebo (41.8%). More venlafaxine ER-treated patients met remission criteria (30%) than placebo-treated patients (19%; P<0.05). The difference was not significant for duloxetine compared to placebo (23%; P value not significant). Sustained improvement rates were greater with duloxetine (55%) and venlafaxine ER (54%) compared to placebo (39%; P<0.01). Duloxetine and venlafaxine ER-treated patients experienced greater improvements in their functioning (SDS global improvement score) from baseline to endpoint compared to placebo (duloxetine, -8.03; venlafaxine ER, -7.97; placebo,-5.42; P<0.01).
Nicolini et al.[170] (2009) Duloxetine 20 mg/day vs duloxetine 60 to 120 mg/day vs	DB, MC, PC, RCT Outpatients ≥18 years of age with GAD	N=581 10 weeks	Primary: HAMA total score Secondary: HAMA psychic and somatic factor scores, SDS, HAMA, CGI-I, PGI-I	Primary: For the HAMA total score, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day, -14.7 [P≤0.01]; duloxetine 60 to 120 mg/day, -15.3 [P≤0.001]; venlafaxine ER, -15.5 [P≤0.001]; placebo -11.6). Secondary: For the HAMA psychic factor scores, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day, -8.1 [P≤0.01]; duloxetine 60 to 120 mg/day, -8.7 [P≤0.001]; venlafaxine ER, -8.6 [P≤0.001]; placebo -6.0).

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venlafaxine ER 75 to 225 mg/day vs placebo				For the HAMA somatic factor score, all three treatments led to improvements from baseline compared to placebo (duloxetine 20 mg/day, -6.6 [P=0.07]; duloxetine 60 to 120 mg/day, -6.6 [P≤0.05]; venlafaxine ER, -7.0 [P≤0.01]; placebo -5.5). Response rates were 60% for duloxetine 20 mg/day (P<0.01), 65% for duloxetine 60 to 120 mg/day (P<0.001), 61% for venlafaxine ER (P<0.001), and 42% for placebo. Remission rates were 42% for duloxetine 20 mg/day, 44% for duloxetine 60 to 120 mg/day, 44% for venlafaxine ER, and 20% for placebo (P<0.001 for each comparisons vs placebo). Overall improvement ratings at endpoint were greater for duloxetine-treated patients (20 or 60 to120 mg/day) and venlafaxine ER-treated patients compared to placebo-treated patients by the CGI-I scores (P<0.001 for all comparisons). All three treatments demonstrated significant improvement on the mean HADS anxiety subscale scores compared to placebo (duloxetine 20 mg/day, -7.0 points; duloxetine 60 to 120 mg/day, -7.7 points; venlafaxine ER, -6.9 points; placebo, -4.9 points; P<0.001 for all comparisons). All three treatments demonstrated significant improvement on the mean HADS depression subscale score compared to placebo (duloxetine 20 mg/day, -3.3 points; duloxetine 60 to 120 mg/day, -3.5 points; venlafaxine ER, -3.6 points; placebo, -1.9 points; P<0.001 for all comparisons). For the SDS global functioning improvement score, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day group, -8.5 [P<0.05]; duloxetine 60 to 120 mg/day, -8.9 [P<0.01]; venlafaxine ER, -9.1 [P<0.001]; placebo, -6.2).
Davidson et al.[171] (2005) Escitalopram 10 to	MC, OL Patients who completed an 8-	N=526 24 weeks	Primary: CGI-I, HAMA core ≤7	Primary: Ninety two percent of the patients were considered responders. Secondary:

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20 mg daily	week, DB, PC, lead-in and were diagnosed with GAD were eligible to enter extension trial		Secondary: Safety	Adverse events led to study withdrawal in 9.9% of patents. The most frequent adverse events leading to study withdrawal were ejaculations disorder (1.6%), insomnia (1.3%), and nausea (1%). Serious adverse events were reported by 2.1% of patients, including one completed suicide.
Goodman et al.[172] (2005) Escitalopram 10 to 20 mg daily vs placebo	DB, MC, PC Patients 18 to 80 years of age with DSM-IV defined GAD	N=850 8 weeks	Primary: HAMA Secondary: CGI-S, CGI-I	Primary: Escitalopram significantly improved mean HAMA total scores (the primary efficacy measure) relative to placebo with the mean change from baseline to week eight in HAMA total score –10.1±0.3 for escitalopram and –7.6±0.3 for placebo (P<0.001). Secondary: Escitalopram led to statistically significant improvements compared to placebo in both HAMA subscales: psychic anxiety (–5.8+0.2 vs –3.9±0.2; P<0.001; and somatic anxiety (–4.3±0.2 vs –3.7±0.2; P=0.02). At endpoint, 47.5% of escitalopram-treated patients and 28.6% of placebo-treated patients were responders (P<0.001), and 26.4% of escitalopram-treated patients and 14.1% of placebo-treated patients were remitters (P<0.001). CGI-I response rates at endpoint were 52% for escitalopram and 37% for placebo (P<0.001).
Strawn et al.[173] (2020) Escitalopram (forced titration to 15 mg/day, then flexible titration to 20 mg/day) vs placebo	DB, RCT Adolescents 12 to 17 years of age with GAD	N=51 8 weeks	Primary: Change in Pediatric Anxiety Rating Scale score from baseline to week 8 and change from baseline in CGI-S and CGI-I response (defined as a CGI-I score of 1 or 2) Secondary:	Primary: At week eight, the mean change in Pediatric Anxiety Rating Scale score in escitalopram-treated patients was −8.65±1.31 compared to −3.52±1.06 in patients receiving placebo (95% CI, −8.57 to −1.70; P=0.005). In the logistic response trajectory model, CGI-I response (i.e., CGI-I ≤2) was greater in escitalopram-treated patients compared to those receiving placebo (P<0.001) and was associated with age (P=0.041) with younger patients experiencing greater improvement. At week eight, 16/26 (62%) escitalopram-treated patients compared to 6/25 (24%) who received placebo had a CGI-I ≤2 (95% CI, 0.95 to 0.578; P=0.0039). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Vital signs, adverse events	Vital signs, corrected QT interval, and adverse events were similar in patients who received escitalopram and placebo.
Strawn et al.[174] (2023) Escitalopram 10 to 20 mg QD (flexibility dosed) vs placebo	DB, MC, RCT Patients 7 to 17 years of age with a primary diagnosis of GAD with PARS-GAD ≥15 at the screening and baseline visits and a CGI-S score ≥4 at the two screening visits	N=275 8 weeks	Primary: Change from baseline to week 8 in PARS-GAD Secondary: Change from baseline to week 8 on the CGAS and CGI-S, response and remission rates at week 8	Primary: Least squares mean (SE) change from baseline to week eight in PARS-GAD was significantly different in favor of escitalopram versus placebo (-7.81 [0.484] vs. -6.38 [0.494]; least squares mean difference=-1.42 [95% CI, 2.69 to -0.15]; P=0.0281). At week two, the difference in least squares mean (SE) change was nominally significant in favor of escitalopram versus placebo (-4.77 [0.389] vs. -3.75 [0.397]; least squares mean difference=-1.02 [95% CI, -2.00 to -0.04]; P=0.0419). Secondary: Least squares mean changes from baseline to week eight in CGAS and CGI-S were numerically greater for escitalopram versus placebo; however, differences did not reach statistical significance. Similarly, the percentages of patients with response (≥50% reduction in PARS-GAD baseline score) and remission (PARS-GAD score ≤8, CGI-S score ≤2, CGAS score >70) at week eight were not significantly different between escitalopram and placebo.
Bielski et al.[175] (2005) Escitalopram 10 to 20 mg/day vs paroxetine 20 to 50 mg/day	DB, RCT Patients with GAD	N=121 24 weeks	Primary: Mean change from baseline in the HAMA scores at week 24, treatment-emergent adverse effects Secondary; Not reported	Primary: After 24 weeks of treatment, patients receiving escitalopram had significantly greater improvement in the HAMA scores compared to the paroxetine group (–15.3 vs –13.3; P=0.13). Significantly fewer patients withdrew from escitalopram than paroxetine treatment due to adverse events (6.6 vs 22.6%; P=0.02). Significantly more patients on paroxetine than on escitalopram experienced treatment-related adverse events (88.7 vs 77.0%). The following adverse events were noted to occur more frequently in the paroxetine group compared to the escitalopram-treated patients: insomnia (25.8 vs 14.8%), constipation (14.5% vs 1.6%), ejaculation disorder (30.0 vs 14.8%), anorgasmia (26.2 vs 5.9%), and decreased libido (22.6 vs 4.9%). In contrast, diarrhea and upper respiratory tract infection were reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				more frequently with escitalopram than paroxetine (21.3 vs 8.1%, and 14.8 vs 4.8%, respectively). Secondary; Not reported
Bose et al.[176] (2008) Escitalopram 10 to 20 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	DB, PC, RCT Outpatients 18 to 65 years of age with GAD	N=404 8 weeks	Primary: Change from baseline to week eight in the HAMA total score Secondary: HAMA psychic anxiety subscale, CGI-I, CGI-S, VAS, HADS QOL, SDS	Primary: The mean change in HAMA total score (LOCF) for escitalopram and venlafaxine ER vs placebo was -1.52 (P=0.09) and -2.27 (P=0.01), respectively at week eight. The mean change in HAMA total score for escitalopram and venlafaxine ER vs placebo was -1.92 (P=0.033) and -3.02 (P=0.001), respectively at week eight. Secondary: Neither escitalopram nor venlafaxine produced greater HAMA response or remission than placebo (response: 52.8 and 52.0% for escitalopram and venlafaxine, respectively vs 42.2% for placebo; remission: 31.2% for both escitalopram and venlafaxine vs 23.7% for placebo; P>0.05 vs placebo, LOCF). Both escitalopram and venlafaxine had significantly higher CGI-I response rates than the placebo (escitalopram 60.0%, venlafaxine 65.6%, placebo 45.9%, P<0.05, LOCF). Both groups had higher CGI-S and HADS response rates compared to placebo. There was no significant difference in VAS, QOL or SDS for escitalopram compared to placebo (LOCF). There was no significant difference in VAS or QOL for venlafaxine compared to placebo (LOCF).
Ball et al.[177] (2005) Paroxetine 10 to 40 mg daily vs sertraline 25 to 100 mg daily	DB, FD, PG Patients with GAD	N=55 8 weeks	Primary: HAMA scores as well as responder and remission rates based on the CGI scale Secondary: Improvement in IU-GAM	Primary: Both sertraline and paroxetine groups displayed significant reductions in HAMA scores from baseline to end of treatment (P<0.001). The mean percent reduction in HAMA scores was 57.3% for the paroxetine group and 55.9% for the sertraline group. The percent of treatment responders was 68% in the paroxetine group and 61% in the sertraline group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Both sertraline and paroxetine groups displayed significant reductions in IU-GAMS scores from baseline to end of treatment (P<0.001). With treatment response defined as a reduction of greater than 50% in IU-GAMS scores from baseline to posttreatment, 40% of the paroxetine group responded compared to 25% of the sertraline group.
Dahl et al.[178] (2005) Sertraline 50 to 150 mg daily vs placebo	MC, RCT Outpatients with GAD	N=373 12 weeks	Primary: Change from baseline to endpoint in HAMA total score of the ITT population Secondary: CGI-S, CGI-I, MADRS, Q-LES-Q	Primary: Sertraline treatment was associated with significant improvement (P<0.001) in the HAMA psychic anxiety factor. Significant separation from placebo in primary endpoint was significant by week 4 for sertraline (52%) compared to placebo (34%; P=0.001). Clinically meaningful improvement (≥30% reduction in psychic symptom severity) was achieved by week four in the majority of patients (P=0001). Secondary: Global improvement was modestly but consistently better correlated with improvement in psychic anxiety. The degree of correlation was similar, regardless of study treatment. QOL was significantly improved in the sertraline group compared to placebo with improvement seen in 51% of patients on sertraline compared to 35% on placebo (P<0.01).
Schmitt et al.[179] (2005) Venlafaxine, paroxetine, imipramine, trazodone, diazepam, sertraline	MA RCTs evaluating antidepressants in GAD	N=2,238 8 to 28 weeks	Primary: Absence of treatment response (defined as absence of sufficient symptoms to meet diagnostic criteria for GAD) Secondary: Acceptability of	Primary: Antidepressants (imipramine, venlafaxine, and paroxetine) were found to be more effective when compared to placebo in treating GAD. The calculated NNT for antidepressants as a group in GAD was 5.15. Considering all trials, the pooled RR for nontreatment response was 0.70 (95% CI, 0.62 to 0.79), favoring antidepressant treatment. The calculated NNT was 5.5 (95% CI, 4.1 to 8.4). For imipramine the calculated RR was 0.67 (95% CI, 0.50 to 0.91) and the NNT was 4.0 (95% CI, 2.4 to 13.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			the treatment as measured by the number of people dropping out during the trial	For venlafaxine the calculated RR for nontreatment response was 0.68 (95% CI, 0.46 to 0.99), and the calculated NNT was 5.00 (95% CI, 3.58 to 8.62). For paroxetine the calculated RR was 0.72 (95% CI, 0.56 to 0.92), and the calculated NNT was 6.72 (95% CI, 3.90 to 24.70). For paroxetine vs imipramine the calculated RR was 1.73 (95% CI, 0.31 to 9.57). Secondary: No significant differences were found between antidepressants and placebo with regard to drop out rate. The RR for dropout for any antidepressant was 0.95 (95% CI, 0.84 to 1.09). Similarly, when individual antidepressants were considered, no differences were found between individual treatments and the placebo group: imipramine: RR, 0.71 (95% CI, 0.41 to 1.24); venlafaxine: RR, 0.86 (95% CI, 0.72 to 1.02); sertraline: RR, 0.45 (95% CI, 0.03 to 5.84); paroxetine: RR, 1.15 (95% CI, 0.74 to 1.78); and paroxetine vs imipramine: RR, 1.62 (95% CI, 0.58 to 4.48).
Insomnia				
Roth et al.[180] (2007) Doxepin 1 mg vs doxepin 3 mg vs doxepin 6 mg	DB, PC, RCT, XO Patients 18 to 64 years of age with chronic primary insomnia	N=67 2 nights	Primary: WTDS Secondary: WASO, sleep efficiency, TST, LPS, number of awakenings after sleep onset, WTAS, and sleep architecture	Primary: WTDS was significantly reduced with doxepin 3 mg (P<0.0001) and doxepin 6 mg (P<0.0001) compared to placebo. There was no significant difference in WTDS with doxepin 1 mg compared to placebo (P=0.0918). Secondary: WASO was significantly decreased with doxepin (all doses) compared to placebo (1 mg; P=0.0090, 3 mg; P<0.0001, and 6 mg; P<0.0001). There were no significant differences in NAASO with doxepin (all doses) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				There was no significant difference in LPS with doxepin (all doses) compared to placebo. TST and overall sleep efficiency were significantly increased with doxepin (all doses) compared to placebo (all P≤ 0.0005). WTAS was significantly reduced with doxepin 6 mg compared to placebo (P=0.0088). There was no significantly difference with doxepin 1 mg (P=0.1421) or doxepin 3 mg (P=0.0697) compared to placebo. WASO was not significantly decreased with doxepin 1 mg (56.4; P=0.8915), doxepin 3 mg (49.4; P=0.8789), or doxepin 6 mg (45.1; P=0.1168) compared to placebo (54.4). Number of awakenings after sleep onset was significantly decreased with doxepin 3 mg (2.8; P=0.0207) compared to placebo (3.2). LSO was significantly decreased with doxepin 6 mg (43.0; P=0.0244), but not significantly decreased with doxepin 1 mg (46.5; P=0.1944) or doxepin 3 mg (45.3; P=0.0905) compared to placebo (49.6). TST was significantly increased with doxepin 6 mg (380.7; P=0.0190), but not with doxepin 1 mg (364.8; P=0.9992) or doxepin 3 mg (380.0; P=0.0562) compared to placebo (364.2). Sleep quality was significantly improved with doxepin 6 mg (0.8; P=0.0071) compared to placebo (0.4). There were no significant differences among doxepin doses for percentage or min of Stage 1 sleep. There was a significant increase in percentage of Stage 2 sleep (3 mg, 57.8%; P=0.0003, 6 mg, 58.7%; P<0.0001; placebo, 54.7%). There was a significant increase in min of Stage 2 sleep (1 mg, 228.5 min; P=0.0008, 3 mg, 240.4 min; P<0.0001, 6 mg, 245.8 min; P<0.0001; placebo, 212.9 min). There was a significant decrease in percentage of REM sleep (3 mg, 18.3%, P=0.0046; 6 mg, 17.8%, P=0.0002; placebo, 20.0%). The number of min spent in REM sleep was not significantly different among the doxepin doses. There were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant differences among doxepin doses for either percentage or min of Stage 3/4 sleep. There were no significant differences among the treatment groups on any of the measures assessing either psychomotor function (DSST) or next-day alertness (VAS). Adverse events were comparable to placebo, with no reported anticholinergic effects, no memory impairment, and no significant hangover/next-day residual effects.
Scharf et al.[181] (2008) Doxepin 1 mg vs doxepin 3 mg vs doxepin 6 mg vs placebo	DB, PC, RCT, XO Elderly patients with primary insomnia	N=76 2 nights	Primary: WTDS Secondary: WASO, TST, sleep efficiency, latency to sleep onset	Primary: Compared to placebo, treatment with doxepin (all doses) led to significant improvements WTDS (P<0.0001). Secondary: Compared to placebo, treatment with doxepin (all doses) led to significant improvements in WASO (P<0.0001). Compared to placebo, treatment with doxepin (all doses) led to significant improvements in TST (P<0.0001). Compared to placebo, treatment with doxepin (all doses) led to significant improvements in overall sleep efficiency (P<0.0001). Sleep efficiency was significantly improved during all thirds of the night with doxepin 3 and 6 mg compared to placebo (P<0.05). Treatment with doxepin 6 mg led to significant improvements in latency to sleep onset compared to placebo (P=0.0181). The incidence of adverse events with doxepin was comparable to placebo.
Krystal et al.[182] (2010) Doxepin 1 mg vs	DB, PC, RCT Patients ≥65 years of age with primary insomnia	N=240 12 weeks	Primary: WASO on night one Secondary: WASO at other	Primary: WASO was significantly improved on night one for doxepin 3 mg (P<0.0001) and doxepin 1 mg (P=0.0053) compared to placebo. Secondary: WASO was significantly improved on night 29 (P=0.0005) night 85

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doxepin 3 mg vs placebo			time points, LPS, number of awakenings after sleep onset, TST, sleep efficiency, and WTAS, CGI-S, CGI-I	(P<0.0001) for doxepin 3 mg, and on night 85 (P=0.0330) for doxepin 1 mg compared to placebo. Mean change from night one to 85 were: placebo, 0.4 (P=0.96); doxepin 1 mg, 3.0 (P=0.57); doxepin 3 mg, 0.9 (P=0.62). TST and overall sleep efficiency were significantly improved on night one (P<0.0001), night 29 (P=0.0161), and night 85 (P=0.0007) for doxepin 3 mg, and on night one (P=0.0119) and night 85 (P=0.0257) for doxepin 1 mg compared to placebo. There was a significant improvement in sTST at weeks one (P=0.0043), four (P=0.0035), and 12 (P=0.0001) for doxepin 3 mg, and at weeks four (P=0.0343) and 12 (P=0.0027) for doxepin 1 mg compared to placebo. Sleep efficiency in the last quarter of the night was significantly increased on night one1 (P<0.0001), night 29 (P=0.0004), and night 85 (P=0.0014) for doxepin 3 mg compared to placebo. For doxepin 1 mg, sleep efficiency in the last quarter of the night was significantly increased on night one (P=0.0011) compared to placebo. Sleep efficiency in hour eight was significantly increased on night one (P<0.0001) and night 29 (P=0.0029) for doxepin 3 mg compared to placebo. For doxepin 1 mg, sleep efficiency in hour eight was significantly increased on night one compared to placebo (P=0.0211). WTAS was significantly decreased on N85 (P=0.0284) for doxepin 3 mg compared to placebo. LPS was not significantly reduced at any time point when compared to placebo. Sleep quality was significantly increased at weeks one (P=0.0039), four (P=0.0049), and 12 (P=0.0100) for doxepin 3 mg, and at weeks four (P=0.0464) and 12 (P=0.0107) for doxepin 1 mg compared to placebo. There was significant improvement after two weeks (P=0.0047), after four weeks (P=0.0356), and after 12 weeks (P=0.0005) on the CGI-S scale

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				score for doxepin 3 mg, and after 12 weeks (P=0.0101) for doxepin 1 mg compared to placebo. There was significant improvement after two weeks (P=0.0060), after four weeks (P=0.0334), and after 12 weeks (P=0.0008) on the CGI-I scale score for doxepin 3 mg, and after 12 weeks (P=0.0082) for doxepin 1 mg compared to placebo. Daytime function ratings were significantly improved on night one for doxepin 3 mg (P=0.0282) and 1 mg (P=0.0192) and on night 85 for doxepin 3 mg (P=0.0028) and 1 mg (P=0.0102) compared to placebo. Sleep stages were preserved compared to placebo, with no apparent evidence of suppression of REM duration. There were no significant differences between placebo and either dose of doxepin on any of the measures assessing objective psychomotor function (DSST) or subjective next-day alertness (VAS) or drowsiness at any time point during the trial. Rates of treatment-emergent adverse events were lower in patients treated with doxepin 1 mg (40%) and doxepin 3 mg (38%) compared to placebo (52%). The most common adverse events were headache and somnolence.
Krystal et al.[183] (2011) Doxepin 3 mg vs doxepin 6 mg vs placebo	DB, PC, RCT Patients 18 to 64 years of age with primary insomnia	N=229 35 days	Primary: WASO on night one Secondary: WASO at other time points, LPS, number of awakenings after sleep onset, TST, sleep efficiency, and	Primary: WASO was significantly improved on night one for doxepin 3 mg (P<0.0001) and doxepin 6 mg (P<0.0001) compared to placebo. Secondary: WASO was significantly improved on night 15 (P=0.0053) and night 29 (P=0.0299) for doxepin 3 mg, and on night 15 (P=0.0023) and night 29 (P=0.0012) for doxepin 6 mg compared to placebo. There were no significant differences between doxepin groups on WASO. TST and sleep efficiency were significantly improved on night one (P<0.0001) and night 29 (P=0.0262) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0157), and night 29 (P=0.0003) for doxepin 6 mg compared to placebo. There were no significant differences in number of awakenings after sleep

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				onset for any dose at any time point. Sleep efficiency in the last quarter of the night was significantly improved on night one (P=0.0008) and night 15 (P=0.0220) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0239), and night 29 (P=0.0029) for doxepin 6 mg compared to placebo. Sleep efficiency in hour eight was significantly improved on night one (P<0.0001) and night 29 (P=0.0315) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0162), and night 29 (P=0.0020) for doxepin 6 mg compared placebo. WTAS was significantly improved on night one (P=0.0001) for doxepin 3 mg, and also on night one (P=0.0016) for doxepin 6 mg compared to placebo. LPS was significantly improved on night one (P=0.0047) for doxepin 3 mg, and on night one (P=0.0007) for doxepin 6 mg compared to placebo. There were significant improvements in patient-reported WASO for both doses of doxepin on night one compared to placebo (3 mg; P=0.0003, 6 mg; P=0.0004). There were significant improvements in patient-reported TST for both doses of doxepin at night one compared to placebo (3 mg; P=0.0088, 6 mg; P=0.0135). Sleep quality was significantly improved for both doses of doxepin at night one compared to placebo (3 mg; P=0.0068, 6 mg; P<0.0001). Subjective LSO was significantly improved on night one with doxepin 6 mg compared to placebo (P=0.0492). There was no evidence of tolerance to the sleep maintenance effects. There is evidence to suggest the development of tolerance to the sleep onset effects. There were increases in the duration of stage two sleep for both doses of doxepin, which were significant at most time points. There were no significant differences between the two doxepin groups vs placebo in minutes of stage one sleep, stage 3/4 sleep, or REM sleep.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Across two nights, rebound insomnia was experienced by 1% of the placebo group, 1% of the doxepin 3 mg group, and 4% of the doxepin 6 mg group.
Roth et al.[184] (2010) Doxepin 6 mg vs placebo	DB, PC, MC, RCT Healthy adults 25 to 55 years of age with normal sleep habits	N=565 Single dose	Primary: LPS Secondary: WASO, TST, WTDS, WTAS, sleep efficiency, and number of awakenings after sleep onset, sleep architecture measurements, DSST, symbol copying test, and VAS	Primary: LPS was significantly lower for doxepin compared to placebo (21 vs 34 minutes, respectively; P<0.0001). Secondary: WASO was significantly lower for doxepin compared to placebo (38 vs 78 minutes, respectively; P<0.0001). WTDS was significantly lower for doxepin compared to placebo (P value not reported). There were no significant differences among the treatment groups in number of awakenings after sleep onset (P value not reported). TST was significantly higher for doxepin compared to placebo (425.2 vs 374.1 minutes, respectively; P<0.0001). Overall sleep efficiency was significantly higher for doxepin compared to placebo (P value not reported). WTAS, sleep efficiency in the final quarter of the night, and sleep efficiency at hours seven and eight were significantly improved for doxepin compared to placebo (all P<0.0001). Doxepin had significantly higher sleep efficiency at each hour compared to placebo (P<0.0001). Subject- reported LSO was significantly lower for doxepin compared to placebo. WASO and sNAASO were significantly lower for doxepin compared to placebo. TST was significantly higher for doxepin compared to placebo. Sleep quality was significantly improved for doxepin compared to placebo. There were no significant differences between doxepin and placebo in the mean change in DSST score from predose to postdose. There were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant differences in sleepiness with doxepin compared to placebo (symbol copying test; P=0.0228, VAS; P=0.0241). The incidence of adverse events with doxepin was comparable to placebo.
Musculoskeletal Pain				
Skljarevski et al.[185] (2010) Duloxetine 60 mg QD vs placebo	DB, PC, RCT Patients ≥18 years of age with chronic low back pain	N=401 12 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: PGI-I, RMDQ-24, CGI-S, BPI-S, BPI-I, response rates, health outcomes (EQ-5D and SF-36)	Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to patients treated with placebo (P≤0.001). Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo-treated patients (2.88 vs 3.19, respectively; P=0.011). There was no significant difference in RMDQ-24 scores with duloxetine compared to placebo (-2.69 vs -2.22, respectively; P=0.255). There was no significant difference in CGI-S among the treatment groups. There was a significant reduction in all four domains of BPI-S (average pain, worst pain, least pain, and pain right now) pain scores reported with duloxetine compared to placebo. All seven domains of the BPI-I (general activity, mood, walking ability, normal work, relations with others, sleep, enjoyment of life) were significantly better with duloxetine compared to placebo. A greater percentage of patients receiving duloxetine reported ≥50% pain reduction compared to patients receiving placebo (P=0.006). There was no significant difference in the 30% pain response rates among the treatment groups. There were significant differences in changes on four of six mood states on the POMS-Brief Form, along with the total mood disturbance score, between the two treatment groups: tension-anxiety (P≤0.001), anger-hostility (P≤0.001), vigor-activity (P=0.003), confusion-bewilderment (P=0.006), and total mood disturbance (P≤0.001). Changes in depression-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				dejection and fatigue-inertia states were not significant. The change in EQ-5D was significantly different between duloxetine and placebo with the United Kingdome index (P≤0.001) and United States index (P=0.002). In the SF-36 domains, the differences between duloxetine and placebo treatments were significant with regard to mental component summary (P=0.010), bodily pain (P=0.016), mental health transformed (P≤0.001), social functioning (P=0.030), and vitality transformed (P=0.022). There was no significant difference among the treatment groups in other domains. The WPAI questionnaire demonstrated a significant difference between the treatment groups with regard to activity impairment (P=0.007). There was no significant difference among the treatment groups in other domains. Significantly more patients in the duloxetine group (15.2%) than patients in the placebo group (5.4%) discontinued because of adverse events (P=0.002). Nausea and dry mouth were the most common treatment-emergent adverse events with rates significantly higher in duloxetine-treated patients.
Skljarevski et al.[186] (2010) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with chronic low back pain	N=236 13 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36), WPAI	Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to patients treated with placebo at all time points (-1.42 vs -0.78, respectively; P=0.016 at week four; -2.06 vs -1.17, respectively; P=0.001 at week seven; and -2.32 vs -1.50, respectively; P=0.004 at week 13). Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo-treated patients at all time points (3.12 vs 3.51, respectively; P=0.007 at week four; 2.82 vs 3.32, respectively; P=0.001 at week seven; 2.59 vs 3.16, respectively; P=0.001 at week 13). There was a significant difference in RMDQ-24 scores at endpoint with duloxetine compared to placebo (-3.60 vs -1.93, respectively; P=0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean changes in pain scores, including BPI-S (worst pain, least pain, and pain right now) items; BPI-I average pain; and weekly mean of the 24-hour average pain, night pain, and worst pain scores from patient diaries were significantly improved with duloxetine compared to placebo. There was no significant difference in the CGI-S and Athens Insomnia Scale scores among the treatment groups. There was no significant difference in response rates with duloxetine compared to placebo (30% response: 53.2 vs 40.0%, respectively; P=0.060 and 50% response: 38.5 vs 27.0%, respectively; P=0.087). The depression and anxiety scores were not significantly changed from baseline to endpoint. The improvement in BPI average pain was because of the direct analgesic effect (80.4%; P=0.012) of duloxetine treatment and not dependent on the improvement in mood (BDI-II total score, 19.2%) or anxiety (HADS-A, 0.3%) symptoms. The United Kingdome and United States indexes of EQ-5D did not change significantly in patients treated with duloxetine compared to patients treated with placebo. Among the eight subscales of SF-36 only bodily pain (P=0.038), general health (P=0.041), and vitality (P=0.040) were significantly improved with duloxetine compared to placebo. In the WPAI, work activity impairment was the only item that significantly (P=0.002) improved with duloxetine compared to placebo. Significantly more patients in the duloxetine group (13.9%) compared to the placebo group (5.8%) discontinued because of adverse events (P=0.047). The most common treatment-emergent adverse events in the duloxetine group included nausea, dry mouth, fatigue, diarrhea, hyperhidrosis, dizziness, and constipation.
Skljarevski et al.[187] (2010) Duloxetine 60 to 120 mg QD	ES Patients ≥18 years of age with chronic low back pain	N=181 41 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating)	Primary: For patients who received duloxetine during the initial 13-week trial, pain reduction continued during the extension phase. The mean change in BPI average pain in the extension phase was -0.97 (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Response rates, PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36)	Secondary: The 30%, 50%, and sustained response rates were ~10% higher for patients who received duloxetine during the initial 13-week trial compared to those who received placebo. A total of 94.8% of PC phase duloxetine responders still met response criteria at the end of the 41-week extension phase. The BPI average pain, worst pain, least pain, pain right now, and average interference all showed significant within-group improvement for both treatment groups. Both treatment groups showed significant improvement on the RMDQ-24 measures, CGI-S measures, and most of the health outcome assessments. No significant change was observed in the BDI total score and HADS depression score. Duloxetine was well tolerated with no new safety findings reported.
Skljarevski et al.[188] (2009) Duloxetine 20, 60, or 120 mg/day vs placebo	DB, MC, PC, RCT Adult patients with non-radicular chronic low back pain	N=404 13 weeks	Primary: Weekly mean 24-hour average pain (duloxetine 60 mg/day vs placebo) Secondary: RMDQ-24, PGI-I, BPI, safety	Primary: Improvement in average weekly pain was significantly greater for duloxetine 60 and 120 mg/day doses beginning at week three, but the significance was lost at weeks 12 and 13, respectively. The mean change from baseline to endpoint in average weekly pain did not differ significantly from placebo for 60 mg/day (P=0.104) or any other duloxetine doses. Analysis of average weekly pain response rates (30% reduction from baseline to end-point) showed a significantly greater percentage of responders with duloxetine 120 mg/day (57.8%) compared to placebo (43.4%; P=0.033), but neither 20 (41.1%) or 60 mg/day (53.6%) differed significantly from placebo (P values not reported). There were no significant differences between any doses in 50% response rates. Secondary: Patients overall improvement (PGI-I) was greater for patients receiving duloxetine 60 mg/day, and improvement in physical functioning (RMDQ-24) was greater for patients receiving duloxetine 60 and/or 120 mg/day

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to patients receiving placebo. Patients receiving duloxetine 60 mg/day also demonstrated significant improvement over patients receiving placebo on several measures of pain severity, interference of pain with activities, and sleep. Eight (1.98%) patients experienced at least one serious adverse event (three placebo-treated patients and one duloxetine 20- and 60 mg/day-treated patients, and three duloxetine 120 mg/day-treated patients). Duloxetine 120 mg/day was associated with a significantly higher proportion of treatment-emergent adverse events compare to placebo (P=0.038).
Chappell et al.[189] (2009) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month	N=231 13 weeks	Primary: Mean changes in the weekly mean 24-hour average pain score Secondary: Patients' perceived improvement as measured by PGI-I and on the change in patients' functioning as measured by the WOMAC physical functioning subscale, weekly mean of the 24-hour worst pain score, CGI-S, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety	Primary: Duloxetine was more effective than placebo on the primary efficacy measure (weekly mean 24-hour pain scores) beginning at week one and continuing through the treatment period (P<0.05). There was a significant reduction in the average pain score in the duloxetine group compared to the placebo group at each week. The mean change from baseline to endpoint in the 24-hour average pain score also showed a significant benefit for duloxetine over placebo (P=0.006). Analysis of the weekly 24-hour average pain score response rates (30% reduction in score from baseline to endpoint) showed a significant difference between duloxetine (59.3%) and placebo (44.5%; P=0.033). The 50% response rates revealed a similar pattern (duloxetine, 47.2%; placebo, 29.4%; P=0.006). Secondary: There was a significant improvement with duloxetine in most secondary endpoints compared to placebo. Mean changes in BDI-II and HADS-A did not differ significantly between treatment groups. For patients randomly re-assigned to duloxetine at week seven, there was a significant improvement in mean change in the weekly 24-hour average pain score in the duloxetine 120 mg/day group compared to the duloxetine 60 mg/day group (P=0.039). No significant differences were observed between the two duloxetine groups in the Mixed Model Repeated Measures analysis of the weekly 24-hour average pain score or the 30%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 50% response rates at endpoint. Adverse event rates did not differ significantly between treatment groups (49.5% for duloxetine and 40.8% for placebo). A total of 45.0% of patients reported ≥1 treatment-emergent adverse events.
Chappell et al.[190](2010) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month	N=256 13 weeks	Primary: BPI 24-hour average pain rating Secondary: Weekly mean 24-hour average pain and worst pain rating, patients' perceived improvement as measured by PGI-I and on the change in patients' functioning as measured by the WOMAC physical functioning subscale, CGI-S, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety	Primary: There was a significant reduction in the BPI average pain rating with duloxetine compared to placebo at all time points (P≤0.001). The BPI average pain response rates (≥30% pain reduction from baseline to endpoint) were significantly higher with duloxetine (65.3%) compared to placebo (44.1%; P≤0.001). The 50% response rates of BPI average pain did not significantly differ between the treatment groups (duloxetine, 43.8%; placebo, 32.3%; P=0.068). Secondary: The least squares mean changes in the weekly mean 24-hour average pain rating was significantly reduced with duloxetine compared to placebo as early as at week two and remained significant at all time points. The weekly mean 24-hour worst pain ratings were significantly improved with duloxetine compared to placebo. Patients receiving duloxetine experienced greater improvements in many secondary endpoints compared to placebo, including CGI-S, BPI-S items, and BPI-I items (general activity and normal work). The other BPI-I items (mood, walking ability, relations with other people, sleep, enjoyment of life, and average interference) were not significantly different between the two treatment groups. No significant improvement in PGI-I was observed in the duloxetine group compared to the placebo group (P=0.164). The mean changes from baseline to endpoint were improved significantly for WOMAC total score (P=0.004) and physical functioning subscale (P=0.016) in patients treated with duloxetine compared to placebo. The other two WOMAC subscales (pain and stiffness) did not show significant improvement with duloxetine treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both the United Kingdome and the United States indexes of EQ-5D did not change significantly with either treatment. Physical component summary and three of the subscales of SF-36 were significantly improved with duloxetine compared to placebo. The other SF-36 items (mental component summary, general health, mental health, role-emotional, social functioning, and vitality) were not significantly improved with duloxetine compared to placebo. The frequency of nausea, constipation, and hyperhidrosis were significantly higher in the duloxetine group (P≤0.05). Significantly more duloxetine-treated patients discontinued therapy because of adverse events (P=0.002).
Frakes et al.[191] (2011) Duloxetine 60 to 120 mg QD vs placebo Patients were also required to take an NSAID and PPI.	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month and who were using NSAIDs on most days of the week	N=524 10 weeks	Primary: Weekly mean of the daily average pain rating at week eight Secondary: Endpoint PGI-I, change in WOMAC physical function	Primary: Patients receiving duloxetine experienced significantly greater pain reduction at week eight than those receiving placebo. The estimated mean change was -2.46 for duloxetine compared to -1.55 for placebo (P<0.001). Duloxetine demonstrated greater improvement as early as week one (P<0.01), and at each subsequent week (P<0.001). Secondary: There was no significant difference in the use of acetaminophen as rescue medication for knee pain due to osteoarthritis (P=0.08). The mean PGI-I and the change in the WOMAC physical function scale were significantly different between the duloxetine and placebo groups (P<0.001 for each). Estimated mean improvement in diary-based night pain and worst pain ratings were significantly greater for duloxetine compared to placebo (P<0.001 for each). Duloxetine-treated patients showed greater reductions for each item on the pain and interference ratings on the BPI compared to placebo-treated patients (P<0.001 for each). Mean reductions for the total score and remaining subscale scores (pain and stiffness) of the WOMAC were significantly different (P<0.001 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				each). Treatment with duloxetine was associated with significantly more nausea, dry mouth, constipation, fatigue and decreased appetite than treatment with placebo (P<0.05). Discontinuation due to adverse events occurred more commonly in the duloxetine group than the placebo group (P=0.03).
Van den Driest et al.[192] (2022) Duloxetine 60 QD vs placebo	OL, RCT Patients ≥18 years of age with hip and/or knee osteoarthritis, had chronic pain, and had shown an insufficient response to treatments with NSAIDs, had contraindication for NSAIDs or had previous adverse reactions to NSAIDs	N=133 12 months	Primary: WOMAC pain score at three months after initiation of treatment Secondary: WOMAC pain score at one year after initiation of treatment, quality of life, patient satisfaction and the Outcome Measures in Rheumatology-Osteoarthritis Research Society International responder criteria	Primary: Patients in the duloxetine group reported slightly less pain than patients in the usual care group (adjusted difference -0.58 [95% CI, -1.80 to 0.63]), which was not clinically relevant or statistically significant. Secondary: The WOMAC pain scores at one year also showed a small difference in favor of the duloxetine group compared to the usual care group (adjusted difference -0.26 [95% CI, -1.86 to 1.34]). There was also a small between-group difference in WOMAC function scores at month 3 (adjusted difference -2.10 [95% CI, -6.39 to 2.20]) and at one year (adjusted difference -1.79 [95% CI, -7.22 to 3.64]). There were small differences in the other secondary outcome measures: quality of life, patient satisfaction, and the Outcome Measures in Rheumatology-Osteoarthritis Research Society International responder criteria. None of the differences between the two groups were clinically relevant or statistically significant.
Mazza et al.[193] (2010) Escitalopram 20 mg QD vs duloxetine 60 mg QD	RCT Adult patients with non-radicular chronic low back pain	N=85 13 weeks	Primary: Weekly mean of the 24-hour average pain ratings Secondary: CGI-S and the 36-item SF-36	Primary: The mean change in average weekly pain did not differ significantly between the escitalopram group and duloxetine group (P=0.15). The average weekly pain response rates (30% reduction from baseline to end point) showed no significant difference between the two groups (P=0.12). There were no significant differences between groups in 50% response rates. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both escitalopram and duloxetine demonstrated significant improvement on CGI-S and SF-36. No patient experienced serious adverse events and the incidence of side effects did not differ significantly between treatment groups.
Obsessive-compulsive Disorder (OCD)				
Alaghband-Rad et al.[194] (2009) Fluoxetine 20 mg/day vs citalopram 20 mg/day	DB, RCT Children 8 to 17 years of age with OCD	N=29 6 weeks	Primary: CY-BOCS total score, CGI-OCD, adverse events Secondary; Not reported	Primary: After three weeks of treatment, obsessive-compulsive symptom severity for both groups decreased to a similar extent using the CY-BOCS total scores. Scores decreased for both obsessions and compulsions. CGI scores did not change significantly from baseline in either group. After six weeks of treatment, obsessive-compulsive symptom severity for both groups decreased to a similar extent using the CY-BOCS total scores. Scores decreased for both obsessions and compulsions (P<0.01). CGI scores did not change significantly from baseline in either group (P=NS). The most frequently reported adverse events were headache (3.4%), tremor (6.8%), insomnia (3.4%), hypomanic episode (3.4%) for fluoxetine. Headache (3.4%), hypomanic episode (3.4%) for citalopram. Secondary; Not reported
Koran et al.[195] (1996) Fluvoxamine 100 to 300 mg/day vs clomipramine 100 to 250 mg/day	DB, RCT Patients with OCD	N=79 10 weeks	Primary: Y-BOCS, CGI, HAM-D Secondary; Not reported	Primary: The mean reduction in Y-BOCS for the fluvoxamine group was 30.2% and for the clomipramine group 30.0% (P=NS). At the end of treatment, 56% of fluvoxamine patients were classified as responders (≥25% decrease in Y-BOCS score), compared to 54% of clomipramine patients. Both groups showed steady improvement throughout the study; no statistically significant differences were observed between the groups for any efficacy variable at any time. A similar percentage of patients in both groups withdrew because of adverse events. No serious adverse events related to drug occurred with either drug. Insomnia, nervousness, and dyspepsia were more statistically frequent with fluvoxamine; dry mouth and postural hypotension were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				more frequent with clomipramine. Secondary; Not reported
Mundo et al.[196] (1997) Fluvoxamine 100 to 300 mg daily vs paroxetine 20 to 60 mg daily vs citalopram 20 to 60 mg daily	RCT Patients with OCD	N=30 10 weeks	Primary: NIMH-OC, Y-BOCS, HAM-D, CGI Secondary; Not reported	Primary: No significant differences were noted between the treatment groups. Results performed on NIMH-OC and Y-BOCS obsessions, compulsions, and total scores did not show any significant effect of the variable group (treatment) but only a significant effect of time (NIMH-OC: P=0.000; Y-BOCS obsessions: P=0.000; Y-BOCS compulsions: P=0.000; Y-BOCS total: P=0.000) and no significant effect of their interaction. Similar results were derived from the ANOVA with repeated measures performed on HAM-D total scores (time effect: P=0.000). Secondary; Not reported
Denys et al.[197] (2003) Paroxetine 15 to 60 mg daily vs venlafaxine 75 to 300 mg daily	DB, PG, RCT Patients with OCD	N=150 12 weeks	Primary: Y-BOCS Secondary; Not reported	Primary: Both paroxetine and venlafaxine were efficacious with a mean decrease of 7.8 and 7.2 points, respectively, at the end of the study, as measured by the reduction in total Y-BOCS scores. Analyses of covariance, adjusted for the mean baseline Y-BOCS scores, revealed a highly significant treatment effect over the 12-week trial period for both treatment groups (P=0.001). A significant decrease in total Y-BOCS scores from baseline was found in the venlafaxine group at week three (P=0.008), whereas in the paroxetine group, a significant decrease in total Y-BOCS scores from baseline was evident as of the fifth week of treatment (P=0.018). Significant decreases in total Y-BOCS scores for both medications were observed until week 10, whereas from week 10 till week 12, no further decrease was detected. Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Panic Disorder				
Stahl et al.[198] (2003) Citalopram vs escitalopram vs placebo	DB, PC, RCT Patients 18 to 80 years of age diagnosed with panic disorder	N=366 10 weeks	Primary: Frequency of panic attacks at week 10 assessed by the Modified Sheehan Panic and Anticipatory Anxiety Scale Secondary; Not reported	Primary: A significant decrease in the frequency of panic attacks was observed in both the escitalopram and citalopram groups compared to placebo (P<0.05). Secondary; Not reported
Dannon et al.[199] (2007) Citalopram 10 to 40 mg/day vs fluoxetine 10 to 40 mg/day vs fluvoxamine 50 to 200 mg/day vs paroxetine 10 to 40 mg/day	OL Adult patients with panic disorder or panic disorder with agoraphobia	N=200 12 months	Primary: Panic Self-Questionnaire, CGI-I Secondary; Not reported	Primary: Following 52 weeks of therapy, the clinical improvements observed were similar between the groups and there were no significant differences in treatment response as measured using the Panic Self-Questionnaire (P=0.13), VAS (P=0.43), or CGI-I (P=NS). There were no significant differences between the panic disorder and the panic disorder with agoraphobia groups in treatment response as measured at the 12 monthly follow-up visits. Secondary; Not reported
Rampello et al.[200] (2006) Escitalopram	OL Elderly patients diagnosed with	N=40 8 weeks	Primary: Weekly rate of panic attacks	Primary: No significant difference was observed at eight weeks in the weekly rate of panic attacks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs citalopram	panic attacks		Secondary: Change from base-line in HAMA, HAMD and Cooper Disability Scale scores	Secondary: No significant differences were observed at eight weeks in the HAMA or HAMD, or in the Cooper Disability Scale scores. A significant improvement from baseline in outcome measures was observed in the escitalopram at two weeks and in the citalopram group at four weeks (P<0.001 and P<0.01 respectively).
Van Ameringen et al.[201] (2007) Nefazodone 300 to 600 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with GSP diagnosis confirmed by DSM-IV for more than 1 year	N=105 14 weeks	Primary: Percent of responders at endpoint Secondary: Not reported	Primary: At endpoint, 31.4% of nefazodone-treated patients and 23.5% of placebo-treated patients were considered responders (P=0.38). Secondary: Not reported
Sheehan et al.[202] (2005) Paroxetine CR 25 to 75 mg daily vs placebo	DB, MC, PC, RCT Patients with DSM-IV panic disorder with or without agoraphobia	N=889 10weeks	Primary: Patients free of panic attacks in the two weeks prior to endpoint Secondary: CGI-I, HAMA	Primary: Paroxetine CR was statistically more effective compared to placebo on the primary outcome measure: 63 vs 53%; P<0.005. Secondary: Paroxetine CR was statistically more effective compared to placebo in the proportion of patients with improved CGI-I (79 vs 55%; P<0.001). Paroxetine CR was statistically more effective compared to placebo in alleviating general anxiety symptoms as measured by HAMA; P<0.001. Adverse events leading to study withdrawal occurred in 11% of patients in the paroxetine CR group and 6% of patients in the placebo group.
Ballenger et al.[203] (1998) Paroxetine 10 mg daily vs	DB, PG, PC, RCT Patients with panic disorder 18 years of age or older	N=278 10 weeks	Primary: Change in panic attacks from baseline, CGI-S Secondary: Marks-Sheehan	Primary: The percent of patients free of panic attacks were 86% (40 mg), 65.2% (20 mg), and 67.4% (10 mg) (P<0.019 at weeks four and 10). No significant differences were noted between groups in mean change from baseline in number of full panic attacks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
paroxetine 20 mg daily vs paroxetine 40 mg daily			Phobia Scale, HARS, MASDR	No significant differences were reported between groups in percentage of patients with a 50% reduction from baseline in number of full panic attacks. The mean CGI global and severity ratings were 81.2% (40 mg), 75.4% (20 mg), 57.8% (10 mg), 51.5% (placebo) (significantly higher with 40 and 20 mg, P<0.019). Secondary: The mean score for public avoidance on the Marks-Sheehan Phobia Scale declined in all groups (P=NS). Significant improvement in the score on the HARS (total) was observed for the 40 mg paroxetine group (in the end-point but not in the completer analysis). Improvement in depressive symptoms (MADRS) was significantly greater for the 40 mg paroxetine group than for the placebo group at week 10.
Bandelow et al.[204] (2004) Sertraline 50 to 150 mg daily vs paroxetine 40 to 60 mg daily	DB, MC, PG, RCT Patients with panic disorder between 18 and 65 years of age	N=225 12 weeks	Primary: Clinician-rated PAS Secondary: CGI-I score	Primary: Treatment with sertraline and paroxetine resulted in equivalent levels of improvement on the primary outcome measure from baseline, the PAS total score (P=0.749). The efficacy of sertraline and paroxetine was equivalent (P=0.487) with regard to the PAS across the agoraphobia and non-agoraphobia subtypes. Secondary: Global response (CGI-I score ≤2) was achieved by 82% of the efficacy-evaluable population treated with sertraline compared to 78% of patients treated with paroxetine (P=0.320).
Pollack et al.[205] (2007) Venlafaxine ER 75 mg/day vs	DB, MC, PC, RCT Outpatients ≥18 years of age with panic disorder (with or without agoraphobia)	N=653 12 weeks	Primary: Percentage of patients free from full-symptom panic attacks at endpoint (LOCF)	Primary: Each of the active treatment groups had a significantly higher proportion of patients who were free of full-symptom panic attacks than in the placebo group (venlafaxine ER 75 mg, 64.7% [P≤0.001 vs placebo]; venlafaxine ER 225 mg, 70.0% [P≤0.001 vs placebo; P≤0.05 vs paroxetine]; paroxetine, 58.3% [P≤0.05 vs placebo]; placebo, 47.8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
venlafaxine ER 225 mg/day vs paroxetine 40 mg/day vs placebo			Secondary: Changes from baseline in the Panic Disorder Severity Scale total score and panic attack frequency	Secondary: All three treatment groups had significantly greater mean reductions in Panic Disorder Severity Scale total score compared to the placebo group at study endpoint. The venlafaxine ER 225 mg group had a significantly lower Panic Disorder Severity Scale total score (4.78 vs 6.26; P<0.05) at endpoint than the paroxetine group. Each of the active treatment groups had significantly more CGI-I responders than the placebo group (venlafaxine ER 75 mg, 81.4%; venlafaxine ER 225 mg, 85.0%; paroxetine, 83.3%; placebo, 59.9%; P<0.001 vs placebo for all comparisons). The percentage of patients who experienced remission was higher in the active treatment groups (venlafaxine ER 225 mg, 50.0%; venlafaxine ER 75 mg, 41.0%; paroxetine 40 mg, 39.3%) than in the placebo group (26.8%).
Posttraumatic Stress Disorder (PTSD)				
Davidson et al.[206] (2005) Fluoxetine 10 to 60 mg daily vs placebo	OL, RCT Patients 18 to 70 years of age with PTSD	N=123 6 months	Primary: Rate of relapse defined by a change in CGI-I score that reverted back to no improvement relative to baseline or worse, CGI-I score which increased by at least two points Secondary: CGI-S	Primary: On the CGI-I, there was a significantly higher number of relapses in the group who received placebo (50%) compared to the group that received fluoxetine (22.2%; P=0.029). Secondary: Differences between the fluoxetine and the placebo group failed to meet significance for CGI-S (P=0.08).
Friedman et al.[207] (2007) Sertraline 250 to 200 mg daily	DB, PC, RCT Patients with combat-related PTSD	N=169 12 weeks	Primary: Mean change in CAPS-2 total severity score from baseline to	Primary: The adjusted mean changes on the CAPS-2 total severity score for the sertraline and placebo groups were –13.1 and –15.4, respectively; the difference was not statically different (P=0.26).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			endpoint Secondary: IES, CGI-S	Secondary: The adjusted mean changes for the IES total score were –8.7 and –8.1 for the sertraline and placebo groups, respectively. The difference was not statistically significant (P=0.28). For the CGI-S scale, there was no statically significant difference between treatment groups in changes from baseline to endpoint. The mean changes from baseline to endpoint were –0.5 and –0.6, respectively (P=0.41).
Premenstrual Dysphoric Disorder				
Pearlstein et al.[208] (2005) Paroxetine CR 12.5 mg daily or 25 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 45 years of age who had regular menstrual cycles with PMDD	N=47 3 menstrual cycles	Primary: VAS-Mood Secondary: VAS-Total	Primary: A statistically significant difference was observed in favor of paroxetine CR 25 mg vs placebo on the VAS-Mood (P<0.001) and for paroxetine CR 12.5 mg vs placebo (P=0.013). Secondary: Paroxetine CR demonstrated greater mean reduction in VAS-Total scores compared to placebo at each time point. At the treatment cycle three last-observation-carried-forward endpoint, statistically significant differences in mean changes were observed in favor of paroxetine CR 25 mg vs placebo (P<0.001) as well as for paroxetine CR 12.5 mg vs placebo (P=0.011).
Steiner et al.[209] (2005) Paroxetine CR 12.5 mg daily vs paroxetine CR 25 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 45 years of age who had regular menstrual cycles with PMDD	N=373 3 menstrual cycles	Primary: VAS-Mood Secondary: Change form baseline to treatment cycle three in the sum of the 11VAS symptoms; change from baseline in the SDS total score	Primary: A statistically significant difference was demonstrated in favor of paroxetine CR 25 and 12.5 mg compared to placebo (paroxetine CR 25 mg vs placebo: adjusted mean difference, –10.79 mm; 95% CI, –16.46 to –5.12; P<0.001; paroxetine CR 12.5 mg vs placebo: adjusted mean difference, –7.66 mm; 95% CI, –13.25 to –2.08; P=0.007) for change from baseline in mean luteal phase VAS-Mood score at the treatment cycle three last-observation-carried-forward endpoint. Secondary: The mean change from baseline in the VAS-Total score, (paroxetine CR 25 mg vs placebo, -77.82 mm; P=0.006, paroxetine CR 12.5 mg vs placebo, –73.13 mm; P=0.009) The mean change from baseline in the SDS total score (paroxetine CR 25 mg vs placebo, –2.74 mm; P=0.016, paroxetine CR 12.5 mg vs placebo,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				–2.33 mm; P=0.028) was greater compared to placebo.
Yonkers et al.[210] (2015) Sertraline 50 to 100 mg/day during the symptomatic interval vs placebo	DB, MC, PC, RCT Women 18 to 48 years of age with menstrual cycles of 21 to 35 days with PMDD	N=252 6 menstrual cycles	Primary: PMTS Secondary: IDS, DRSP, Michelson SSRI Withdrawal Scale	Primary: The difference between the sertraline and placebo groups in rates of change for the PMTS scores was not statistically significant (P=0.06). Secondary: Compared with the placebo group, participants in the sertraline group showed greater improvement in IDS scores over time (P=0.02). The mean changes in the total and Anger/Irritability subscale scores of the DRSP were greater for the sertraline than the placebo groups, with an estimated mean difference for change from baseline to the end point for the total DRSP (1.09; 95% CI, 0.96 to 1.25; P=0.02) and the Anger/Irritability subscale (1.22; 95% CI, 1.05 to 1.41; P<0.01) scores, but no differences were found between conditions in the Depressive Symptoms and Physical Symptoms subscales. Both groups acknowledged fewer and similar symptoms on the Michelson SSRI Withdrawal Symptoms Scale as the trial progressed.
Multiple Diseases				
Wernicke et al.[211] (2007) Duloxetine vs placebo	MA (42 RCTs) Patients diagnosed with either an MDD, diabetic peripheral neuropathy, fibromyalgia, GAD, or lower urinary tract infection	N=8,504 4 to 12 weeks	Primary: Vital signs, ECG findings, cardiovascular side effects of the study drug Secondary: Not reported	Primary: Patients receiving duloxetine were noted to have statistically significant changes from baseline in ECG findings compared to patients receiving placebo (P<0.001). However, the differences in ECG findings of patients taking duloxetine were not judged to be of clinical significance. Demographic subgroup analysis suggests that there is no difference in risk of ECG abnormality or vital sign changes between patients ≥65 years of age and a younger population (P value not reported). Although patients receiving duloxetine experienced statistically significant pulse and blood pressure elevations compared to patients receiving placebo (P<0.001), those changes were transient returning to baseline values with sustained therapy. There was no statistically significant difference between placebo and duloxetine groups in sustained blood pressure (P=0.631), SBP (P=0.740), or DBP (P=1.00) measured during three consecutive visits.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients randomized to duloxetine therapy experienced higher incidences of palpitations (P=0.004), tachycardia (P=0.007), orthostatic hypotension (P=0.004), increased blood pressure (P<0.001), blood total cholesterol (P=0.031), and peripheral coldness (P=0.044) compared to patients randomized to placebo. Secondary: Not reported
Mullins et al.[212] (2005) Sertraline vs paroxetine vs citalopram	RETRO Patients with depression, PTSD, or social anxiety disorder	N=14,933 Data gathered from 1/1/99 to 6/30/02	Primary: Persistence, switching, discontinuation Secondary: Not reported	Primary: Compared to patients receiving sertraline and citalopram, those receiving paroxetine had lower rates of persistence (23.79% for paroxetine vs 25.96% for sertraline [P=0.0093] and 26.56% for citalopram [P=0.0022]) and higher rates of switching (3.55% for paroxetine vs 3.32% for sertraline [P=0.5076] and 2.78% for citalopram [P=0.0359]) and discontinuation (72.66% for paroxetine vs 70.72% for sertraline [P=0.0258] and 70.66% for citalopram [P=0.0334]). Survival curves showed that persistence rates with sertraline and citalopram were significantly greater than with paroxetine (P<0.05). Secondary: Not reported
Stein et al.[213] (2000) SSRIs, MAOIs, benzodiazepines, beta blockers, buspirone, gabapentin, olanzapine	MA Patients with social anxiety disorders	N=5,264 (36 trials) Variable duration	Primary: CGI-I scale Secondary: LSAS	Primary: Summary statistics for responder status (assessed using the CGI from 25 short-term comparisons demonstrated a higher degree of efficacy of various medications over placebo (RR of non-response, 0.63; 95% CI, 0.55 to 0.72). Response to treatment by SSRIs (N=11; RR, 0.67; 95% CI, 0.59 to 0.76), MAOIs (N=3; RR, 0.43; 95% CI, 0.24 to 0.76) supported the value of these agents. However, the SSRIs were significantly more effective than the other agents (P<0.00001). Secondary: LSAS showed a statistically significant difference between medication and placebo (weighed mean difference, –15.56; 95% CI, –17.95 to -13.16), with this effect once again most evident for the SSRIs.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Medication was also significantly more effective compared to placebo in reducing symptom clusters, comorbid depressive symptoms, and associated disability. The value of long-term medication treatment in treatment responders was supported by three comparisons from maintenance studies (RR, 0.58; 95% CI, 0.39 to 0.85) and five comparisons from relapse prevention studies (RR, 0.33; 95% CI, 0.22 to 0.49).

Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended release, QD=once daily, SR=sustained release, XR=extended release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, ES=extension study, FD=fixed dose, ITT=intention to treat, LOCF=last observation carried forward, LSM=least square mean, LSMD=least square mean difference, MA=meta-analysis, MC=multicenter, NI=non inferiority, NNH=number needed to harm, NNT=number needed to treat, OBS=observational, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, SC=single center, SE=standard error, SMD=standard mean difference, SR=systemic review, XO=cross over
Diagnostic Criteria: DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition
Miscellaneous abbreviations: ASEX=Arizona Sexual Experience Scale, BAI=Beck Anxiety Inventory, BDI-FS=Beck Depression Inventory Fast Screen, BDI-II=Beck Depression Inventory-II, BPI=brief pain inventory, CAPS-S=Clinician-Administered PTSD Scale, CES-D=Center for Epidemiological Studies-Depression Scale, CGI-I=Clinical Global Impression, Improvement, CGI-S=Clinical Global Impression, Severity, CSFQ=Changes in Sexual Functioning Questionnaire, DBP=diastolic blood pressure, DRSP=Daily Record of Severity of Problems, DSST=digital symbol substitution test, ECG=electrocardiogram, EQ-5D=EuroQoL: 5 Dimensions Questionnaire, FIQ=Fibromyalgia Impact Questionnaire, FIQ=Fibromyalgia Impact Questionnaire-Revised, GAD=Generalized Anxiety Disorder, GAF=Global Assessment of Functioning, GDS=Geriatric Depression Scale, GSP=Generalized Social Phobia, HADS-A=Hospital Anxiety and Depression Scale – Anxiety subscale, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, HARS=Hamilton Anxiety Rating Scale, HDRS-17=17-item Hamilton Depression Rating Scale, HRQOL=health related quality of life, IDS=Inventory of Depressive Symptomatology-Clinician-Rated, IES=Impact of Event Scale, IU-GAM=Indiana University Generalized Anxiety Measurement Scale, LANSS=Leeds Assessment of Neuropathic Symptoms and Signs, LPS=Latency to Persistent Sleep, LSAS=Liebowitz Social Anxiety Scale, MADRS=Montgomery-Åsberg Depression Rating Scale, MAOIs=Monoamine Oxidase Inhibitors, MDD=major depressive disorder, MFI=Multidimensional Fatigue Inventory, MHID=Mantel-Haenszel Incidence Difference, MHRD=Mantel-Haenszel Exposure Time-adjusted Rate Difference, MRS=Menopause Rating Scale, NIMH-OC=National Institute of Mental Health-Obsessive-Compulsive Scale, NSAID=nonsteroidal anti-inflammatory drug, OCD=obsessive compulsive disorder, PAS=Panic and Agoraphobia Scale, PGI-C=Patient Global Impression of Change, PGI-I=Patient Global Impressions of Improvement, PMDD=premenstrual dysphoric disorder, PMTS=Premenstrual Tension Scale, PPD=postpartum depression, PPI=proton pump inhibitor, PTSD=Posttraumatic Stress Disorder, QIDS= Quick Inventory of Depressive Symptomatology, QIDS-SR16=16-item Quick Inventory of Depressive Symptomatology–Self-Rated, QOL=Quality of Life, Q-LES-Q=Quality of Life, Enjoyment, and Satisfaction Questionnaire, RAVLT=Rey Auditory Verbal Learning Test, REM=rapid eye movement, RMDQ-24=Roland Morris Disability Questionnaire, SBP=systolic blood pressure, SDS=Sheehan Disability Scale, SF-36=36-item Short-Form Health Status Survey, SNRI=serotonin norepinephrine reuptake inhibitor, SSI=28-item Somatic Symptom Inventory, SSRIs=Selective Serotonin-reuptake Inhibitors, TST=Total Sleep Time, UPDRS=Unified Parkinson's Disease Rating Scale, VAS=Visual Analog Scale, WASO=Wake Time After Sleep Onset, WHO-5=World Health Organization 5-item Well Being Index, WOMAC=Western Ontario and McMaster Universities, WPI=Widespread Pain Index, WTAS=Wake Time After Sleep, WTDS=Wake Time During Sleep, Y-BOCS=Yale-Brown Obsessive-Compulsive Scale

Additional Evidence

Dose Simplification
Claxton et al. evaluated compliance rates with fluoxetine 90 mg once weekly compared to fluoxetine 20 mg once daily in patients who had previously received four weeks of fluoxetine 20 mg once daily.[214] At the end of 12 weeks, compliance significantly declined from 87 to 79% with the once daily fluoxetine; however, the effect on clinical outcomes was not measured. More patients in the once-weekly group discontinued therapy due to lack of efficacy than in the once-daily group, but this difference was not statistically significant.

Stable Therapy
Brent et al. evaluated the efficacy of four treatment strategies in adolescents who continued to have depression despite initial treatment with a selective serotonin-reuptake inhibitor (SSRI).[215] The interventions included switching to a different SSRI, switching to a different SSRI plus cognitive behavioral therapy, switching to venlafaxine, or switching to venlafaxine plus cognitive behavioral therapy. The authors found that switching to a different treatment plus cognitive behavioral therapy was more effective than medication switch alone. A switch to another SSRI was as effective as switching to venlafaxine.

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 Antidepressants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Monoamine Oxidase Inhibitors				
Isocarboxazid	tablet	Marplan®	$$$$$	N/A
Phenelzine	tablet	Nardil®*	$$$$	$$
Selegiline	transdermal patch	Emsam®	$$$$$	N/A
Tranylcypromine	tablet	N/A	N/A	$$$$
Selective Serotonin- and Norepinephrine-reuptake Inhibitors				
Desvenlafaxine	extended-release tablet	Pristiq®*	$$$$$	$$
Duloxetine	delayed-release capsule	Cymbalta®*, Drizalma Sprinkle®	$$$$$	$
Levomilnacipran	extended-release capsule	Fetzima®	$$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Venlafaxine	extended-release capsule, extended-release tablet, tablet	Effexor XR®*	$$$$$	$
Selective Serotonin-reuptake Inhibitors				
Citalopram	capsule, solution, tablet	Celexa®*	$$$$$	$
Escitalopram	solution, tablet	Lexapro®*	$$$$$	$
Fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*	$$$$$	$
Fluvoxamine	extended-release capsule, tablet	N/A	N/A	$$$
Paroxetine	capsule, extended-release tablet, suspension, tablet	Paxil®*, Paxil CR®*, Pexeva®	$$$$$	$
Sertraline	capsule, oral concentrate, tablet	Zoloft®*	$$$$$	$
Serotonin Modulators				
Nefazodone	tablet	N/A	N/A	$$$$$
Trazodone	tablet	N/A	N/A	$
Vilazodone	tablet	Viibryd®*	$$$$$	$$$$
Vortioxetine	tablet	Trintellix®	$$$$$	N/A
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents				
Amitriptyline	tablet	N/A	N/A	$
Amoxapine	tablet	N/A	N/A	$$$
Clomipramine	capsule	Anafranil®*	$$$$$	$$$$
Desipramine	tablet	Norpramin®*	$$$$$	$
Doxepin	capsule, oral concentrate, tablet	Silenor®*	$$$$$	$$
Imipramine	capsule, tablet	N/A	N/A	$
Nortriptyline	capsule, solution	Pamelor®*	$$$$$	$
Protriptyline	tablet	N/A	N/A	$$$$
Trimipramine	capsule	N/A	N/A	$$$$$
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products				
Amitriptyline and chlordiazepoxide	tablet	N/A	N/A	$$$$
Antidepressants, Miscellaneous				
Bupropion	extended-release tablet, sustained-release tablet, tablet	Aplenzin®, Forfivo XL®*, Wellbutrin SR®*, Wellbutrin XL®*	$$$$$	$
Dextromethorphan and Bupropion	tablet	Auvelity ER®	$$$$$	N/A
Esketamine	nasal spray	Spravato®	$$$$$	N/A
Mirtazapine	orally disintegrating tablet, tablet	Remeron®*	$$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa), mood disorders, premenstrual dysphoric disorder, and moderate to severe vasomotor symptoms associated with menopause.[1-3] Some of the agents are also approved for the treatment of nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, nocturnal enuresis, and tobacco abuse.[1-3] The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs),

selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs), and miscellaneous agents. The agents which make up these subclasses differ with respect to their Food and Drug Administration (FDA)-approved indications, mechanism of action, pharmacokinetics, adverse events, and drug interactions. The majority of the products are available in a generic formulation, and there is at least one generic product available in each antidepressant subclass.

Numerous clinical trials have been conducted with the antidepressants and comparative studies have demonstrated similar efficacy in patients with major depressive disorder.[5,24-146] Guidelines do not give preference to one agent over another. Rather, the selection of an antidepressant should be based on adverse events, tolerability, and patient preference.[5,6]

Several antidepressants are approved for the treatment of anxiety disorders. The American Psychiatric Association recommends the initial use of either an SNRI or SSRI for the treatment of panic disorder due to their favorable safety and tolerability profiles.[8] The National Institute for Health and Clinical Excellence recommends the use of SSRIs as first-line therapy for the long-term treatment of generalized anxiety disorder.[8] SSRIs are also recommended for the initial treatment of obsessive-compulsive disorder.[10-11] The SNRIs, SSRIs, and TCAs have all been shown to be more effective than placebo for the treatment of anxiety disorders, and comparative studies have demonstrated similar efficacy among the antidepressants.[165-179,194-205] Guidelines do not give preference to one agent over another.[12-18] The choice of treatment should be based on safety, adverse events, drug interactions, prior response to treatment and comorbid conditions.[8-14]

Duloxetine has been approved by the FDA for the treatment of chronic musculoskeletal pain, in addition to depression, generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia.[1-3] It has been shown to be more effective than placebo in most patients with chronic low back pain and osteoarthritis of the knee; however, the effects were modest.[185-193]

Antidepressants are most commonly prescribed for postpartum depression according to the same principles for other types of major depressive disorder, despite a limited number of controlled studies. Ongoing patient assessments for efficacy and ongoing need for therapy is advised.[5,7] Based upon clinical trials, the least-squares mean reduction in HAM-D total score at the end of the 60-hour intravenous infusion favored brexanolone compared to placebo.[23] Guidelines currently do not specifically address this new agent. Due to safety concerns, brexanolone carries a boxed warning regarding excessive sedation and loss of consciousness, requiring continuous pulse oximetry monitoring. In addition, brexanolone is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program called Zulresso® REMS due to safety concerns.[1-3]

Esketamine was evaluated in placebo-controlled trials among adults with major depressive disorder. Results demonstrated that patients treated with esketamine nasal spray plus an oral antidepressant demonstrated greater improvements in mean MADRS score compared to those treated with placebo plus an oral antidepressant, and among remitters, fewer patients treated with esketamine plus and oral antidepressant experienced a relapse compared to patients treated with placebo.[80-82] Esketamine is associated with significant side effects, and carries a boxed warning regarding sedation, dissociation, abuse, and misuse. Due to these risks, esketamine is only available through a restricted Spravato® REMS program.[1-3]

Auvelity® (dextromethorphan/bupropion) is the first oral N-methyl-D-aspartate (NMDA) receptor antagonist approved by the FDA. Dextromethorphan is an uncompetitive NMDA receptor antagonist/sigma-1 receptor agonist and bupropion is an aminoketone/CYP450 2D6 inhibitor. The exact mechanism of dextromethorphan in the treatment of MDD is unclear. The mechanism of bupropion may be related to noradrenergic and or dopaminergic mechanisms. Bupropion also increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6.[3] FDA approval of Auvelity® was based on two clinical trials that evaluated the safety and efficacy dextromethorphan/bupropion versus bupropion alone (ASCEND) and versus placebo (GEMINI). The ASCEND trial found that the mean change from baseline was -13.7 points with dextromethorphan/bupropion versus -8.8 points with bupropion (P<0.001).[48] The GEMINI trial showed a statistically significantly greater MADRS improvement at all time points including week one (P=0.007) and week two (P<0.001) when compared to placebo. Remission was achieved by 39.5% of patients treated with

dextromethorphan/bupropion versus 17.3% treated with placebo (treatment difference, 22.2; 95% CI, 11.7 to 32.7; P<0.001).[49] The use of Auvelity® is not addressed in current treatment guidelines.

According to the boxed warning, antidepressants increased the risk of suicidal thinking and behavior in children, adolescents and young adults compared to placebo in short-term studies of major depressive disorder and other psychiatric disorders.[1-3] Short-term studies did not show an increase in the risk of suicidality in adults older than 24 years of age, and there was a reduction in risk in adults 65 years of age and older. Although the MAOIs are an effective treatment option for patients with major depressive disorder, drug interactions, dietary restrictions, and serious adverse events limit their use. It is recommended that MAOIs be reserved for patients who are not responding to other treatment options.[5]

There is insufficient evidence to support that one brand antidepressant is 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 antidepressants within the class reviewed, with the exception of the monoamine oxidase inhibitors, are comparable to each other and to the generics in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. The monoamine oxidase inhibitors possess an extensive adverse effect profile compared to the other brands and generics in the class (if applicable) and should be managed through the existing medical justification portion of the prior authorization process. In addition, brexanolone for intravenous administration and esketamine nasal spray are both indicated for specific patient populations, have significant side effect profiles, and are only available through restricted access program and; therefore, should also be managed through the existing medical justification portion of the prior authorization process.

XI. Recommendations

No brand antidepressant 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.

No brand monoamine oxidase inhibitor is recommended for preferred status, regardless of cost.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Review: Veozah® (fezolinetant)
AHFS Class 289200 - Central Nervous System Agents, Miscellaneous
Will be included with AHFS 681604 - Estrogens
February 7, 2024

I. Overview

Veozah® (fezolinetant) is a first-in-class, nonhormonal, selective neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause.[1-3] Fezolinetant blocks neurokinin B binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center, helping to reduce the number and intensity of VMS.[1-3] VMS, commonly known as hot flashes or night sweats, are the most prevalent bothersome symptom in menopause, occurring in up to 80% of women in the United States during the menopausal transition.[4] Menopausal hormone therapy (MHT), consisting of estrogen alone or combined with progestin, is the most effective treatment option in most patients with VMS, and can treat other menopausal symptoms as well.[4-5] For patients with moderate to severe VMS who are unwilling or unable to tolerate MHT, a variety of nonhormonal agents have shown efficacy, including but not limited to selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), antiepileptics, gabapentin, clonidine, and oxybutynin.[4] Veozah® is the second nonhormonal agent to have gained FDA approval for the indication of VMS after Brisdelle® (paroxetine mesylate 7.5 mg); all other nonhormonal therapies are used off-label.[4,6]

The agents that are included in this review are listed in Table 1. Fezolinetant is not available in a generic formulation.

Table 1. Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Fezolinetant	tablet	Veozah®	none

*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 are summarized in Table 2.

Table 2. Treatment Guidelines

Clinical Guideline	Recommendation(s)
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**	<u>Benefit/risk profile of menopausal hormone therapy (MHT)</u> • 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

Clinical Guideline	Recommendation(s)
Consensus Statement on Menopausal Hormone Therapy (2016)[7]	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 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. • 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

Clinical Guideline	Recommendation(s)
	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. General principles governing the use of MHT • 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.
The British Menopause Society, International Menopause Society, European Menopause and Andropause Society, Royal College of Obstetricians and Gynaecologists, and Australasian Menopause Society: **Joint Statement on menopausal hormone therapy (MHT) and breast cancer risk (2020)[8]**	Menopausal symptoms • The menopause transition can have a significant impact on many women, with more than 75% experiencing menopausal symptoms, a quarter describing severe symptoms, and a third experiencing long-term symptoms. Treatments • MHT, compared with placebo, has been consistently shown to improve menopausal symptoms and overall quality of life and remains the most effective treatment for menopausal symptoms. For some women, MHT may not be suitable, and alternative treatments are available. MHT and breast cancer risk - The Collaborative Group on Hormonal Factors in Breast Cancer meta-analysis • Duration-dependent increase in the risk of breast cancer diagnosis with both unopposed estrogen and combined MHT. • The risk is higher with continuous combined MHT regimens compared to cyclical.

Clinical Guideline	Recommendation(s)
	• The risk of breast cancer remains elevated more than 10 years after discontinuing MHT. • No estrogen dosage effect on the risk of breast cancer with MHT. • Vaginal estrogen exposure did not increase the risk of breast cancer diagnosis. • Only a small number of women on micronized progesterone were included. Therefore, conclusions regarding its impact on the risk of breast cancer diagnosis could not be determined from this meta-analysis. • The decision whether to take MHT, the dose of MHT and the duration of its use should be made on an individualized basis after discussing the benefits and risks with women to help them make an informed choice about their health and care. <u>Osteoporosis</u> • Evidence from RCTs and meta-analysis shows that women using MHT have a significant reduction in the risk of any fracture compared with women not using MHT. <u>Cardiovascular disease (CVD)</u> • The timing MHT is initiated, referred to as the 'timing hypothesis' and 'the cardiovascular window of opportunity', can have a significant impact on the risk of CVD with MHT intake. • Cochrane data-analysis shows that MHT initiated within 10 years of menopause is likely to be associated with a reduction in coronary heart disease and cardiovascular mortality. • Evidence from the Cochrane data-analysis and that from the long-term follow-up data of the WHI showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated MHT more than 10 years after the menopause. <u>Risk of venous thromboembolism</u> • Compared with women not on MHT, the risk of venous thromboembolism is increased by oral intake MHT. • Transdermal administration of estradiol is unlikely to increase the risk of venous thrombosis above that in non-users and is associated with a lower risk compared with oral administration of estradiol.
North American Menopause Society: **Management of Osteoporosis in Postmenopausal Women: 2021 Position Statement (2021)[9]**	• Intervening to prevent rapid bone loss and deterioration of skeletal structure is a unique opportunity to maintain bone health. • Such intervention would be most appropriate in women with low bone mineral density (BMD) who are experiencing relatively rapid bone loss because of acute estrogen deficiency in the perimenopausal and early postmenopausal periods or on discontinuing estrogen-alone therapy. • For younger, healthy postmenopausal women, particularly those with vasomotor symptoms, who are candidates for prevention of bone loss, estrogen alone (if no uterus) or combined with progestogen or bazedoxifene are the most appropriate therapies. o A bisphosphonate could be chosen if estrogen is contraindicated or on stopping estrogen-alone therapy. o Raloxifene is a good option for prevention of bone loss in postmenopausal women with an elevated risk of breast cancer and infrequent vasomotor symptoms. • Bisphosphonates to prevent bone loss can be considered in postmenopausal women with low BMD (T-score <1) and other risk factors for fracture (e.g., family history) who do not meet criteria for osteoporosis treatment. • The choice of the initial treatment for osteoporosis is based on the patient's current BMD and fracture risk. • Raloxifene is an option for the treatment of postmenopausal osteoporosis in

Clinical Guideline	Recommendation(s)

	women with a low risk of hip fracture, an elevated risk of breast cancer, and low risk of stroke and venous thromboembolism.
	• Bisphosphonates are appropriate to reduce fracture risk in women with postmenopausal osteoporosis.
	  o Use with caution in patients with significantly impaired renal function.
	  o Consider a bisphosphonate holiday only in women at low fracture risk who no longer meet criteria for therapy. Restart therapy if bone loss or fractures occur or when patient again meets criteria for treatment.
	  o For patients remaining at high fracture risk after three to five years of bisphosphonate therapy, continue treatment or switch to another drug.
	• Denosumab is appropriate for women with postmenopausal osteoporosis, including those at high risk of fracture.
	  o There is no limit to the duration of denosumab therapy.
	  o Administration of denosumab should not be delayed or stopped beyond seven months without subsequent therapy to prevent bone loss and vertebral fractures.
	• Osteoanabolic therapies are most appropriately used in women at very high risk of fracture, including those with prior and especially recent fractures, very low BMD (T-score below 3.0), and those who sustain fractures or lose BMD while taking antiremodeling therapy.
	  o Osteoanabolic therapies increase bone mass more rapidly and reduce fracture risk more effectively than do bisphosphonates.
	  o Anabolic therapy should be followed by an antiremodeling agent to maintain bone density gains.
	  o Bone mineral density gains, particularly in the hip, are greater when an anabolic drug is administered before an antiremodeling drug, compared with the opposite sequence.
	• Bone mineral density measured while on therapy correlates with current fracture risk.
	• If the response to the initial treatment does not achieve preventing bone loss or reducing the risk of fracture, a change in treatment should be considered.
	• If drug-related adverse events occur, appropriate management strategies should be instituted. If adverse events persist, switching to another agent may be required.
	• Identify barriers to nonadherence to therapy and encourage adherence to the treatment plan. Providing clear information to women regarding their risk for fracture and the purpose of osteoporosis therapy may be an optimal way to improve adherence.
	• Depending on the treatment, an appropriate interval for repeat BMD testing is one to two years after beginning treatment or when a change in therapy is considered.
	• Initial dual-energy X-ray absorptiometry (DXA) and follow-up scans should ideally be performed on the same instrument, using the same procedure. Interpretation of BMD changes requires careful attention to DXA quality control.
	• If progressive loss of BMD or fractures occurs while on therapy, evaluate for reasons for suboptimal response to therapy, including poor adherence and underlying medical conditions or medications.
	• Even when treatment increases T-score values above 2.5, the patient still has the diagnosis and risks of osteoporosis.
	• Referral to bone specialists is recommended for women with very low T-scores, inadequate treatment response, including progressive decline in BMD or

Clinical Guideline	Recommendation(s)
	fractures while on therapy, or additional factors (e.g., renal failure, hyperparathyroidism) requiring special management.
North American Menopause Society: **The 2022 Hormone Therapy Position Statement (2022)[10]**	<u>Formulation, dosing, routes of administration, and safety</u> • The appropriate, often lowest, effective dose of systemic estrogen therapy consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal. • The various formulations, doses, and routes of prescription hormone therapy preparations have comparable high efficacy for relieving vasomotor symptoms. • Formulation, dose, and route of administration for hormone therapy should be determined individually and reassessed periodically. • Different hormone therapy doses, formulations, and routes of administration may have different effects on target organs, potentially allowing options to minimize risk. • The appropriate formulation, dose, and route of administration of progestogen is needed to counter the proliferative effects of systemic estrogen on the endometrium. • Overall, the increased absolute risks associated with estrogen plus progestogen therapy (EPT) and estrogen therapy are rare (<10/10,000/y) and include increased risk for venous thromboembolism (VTE) and gallbladder disease. In addition, EPT carries a rare increased risk for stroke and breast cancer, and if estrogen is inadequately opposed, an increased risk of endometrial hyperplasia and endometrial cancer. • The absolute risks are reduced for all-cause mortality, fracture, diabetes mellitus (EPT and estrogen therapy), and breast cancer (estrogen therapy) in women aged younger than 60 years. <u>Compounded bioidentical hormones</u> • Compounded bioidentical hormone therapy presents safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks. • Salivary and urine hormone testing to determine dosing are unreliable and not recommended. Serum hormone testing is rarely needed. • Shared decision-making is important, but patient preference alone should not be used to justify the use of compounded bioidentical hormone preparations, particularly when government-regulated bioidentical hormone preparations are available. • Situations in which compounded bioidentical hormones could be considered include allergies to ingredients in a government-approved formulation or dosages not available in government-approved products. <u>Vasomotor symptoms</u> • Vasomotor symptoms may begin during perimenopause, and frequent vasomotor symptoms may persist on average 7.4 years or longer. They affect quality of life and may be associated with cardiovascular (CV), bone, and brain health. • Hormone therapy remains the gold standard for relief of vasomotor symptoms. • Estrogen-alone therapy can be used for symptomatic women without a uterus. • For symptomatic women with a uterus, EPT or a tissue-selective estrogen complex protects against endometrial neoplasia. • Shared decision-making should be used when considering formulation, route of administration, and dose of hormone therapy for menopause symptom management, with adjustment tailored to symptom relief, adverse events, and patient preferences. • Periodic assessment of the need for ongoing use of hormone therapy should be

Clinical Guideline	Recommendation(s)
	individualized on the basis of a woman's menopause symptoms, general health and underlying medical conditions, risks, treatment goals, and personal preferences. • Micronized progesterone 300 mg nightly significantly decreases vasomotor symptoms (hot flashes and night sweats) compared with placebo and improves sleep. Synthetic progestins have also shown benefit for vasomotor symptoms in some studies. No long-term study results are available, and use of progestogens without estrogen for either indication is off-label. <u>Sleep disturbances</u> • During the menopause transition, women with vasomotor symptoms are more likely to report disrupted sleep. • Hormone therapy improves sleep in women with bothersome nighttime vasomotor symptoms by reducing nighttime awakenings. Estrogen may have some effect on sleep, independent of vasomotor symptoms. <u>Genitourinary symptoms</u> • Low-dose vaginal estrogen therapy preparations are effective and generally safe for the treatment of genitourinary syndrome of menopause, with minimal systemic absorption, and are preferred over systemic therapies when estrogen therapy is used only for genitourinary symptoms. • For women with breast cancer, low-dose vaginal estrogen therapy should be prescribed in consultation with their oncologists. • Progestogen therapy is not required with low-dose vaginal estrogen, but RCT data are lacking beyond one year. • Nonestrogen prescription FDA-approved therapies that improve vulvovaginal atrophy in postmenopausal women include ospemifene and intravaginal DHEA. • Vaginal bleeding in a postmenopausal woman requires thorough evaluation. <u>Urinary tract symptoms (including pelvic floor disorders)</u> • Systemic hormone therapy does not improve urinary incontinence and may increase the incidence of stress urinary incontinence. • Low-dose vaginal estrogen therapy may provide benefit for urinary symptoms, including prevention of recurrent UTIs, overactive bladder, and urge incontinence. • Hormone therapy does not have FDA approval for any urinary health indication. <u>Sexual function</u> • Both systemic hormone therapy and low-dose vaginal estrogen therapy increase lubrication, blood flow, and sensation of vaginal tissues. • Systemic hormone therapy generally does not improve sexual function, sexual interest, arousal, or orgasmic response independent of its effect on genitourinary syndrome of menopause. • If sexual function or libido are concerns in women with menopause symptoms, transdermal estrogen therapy may be preferable over oral estrogen therapy because of minimal effect on sex hormone-binding globulin and free testosterone levels. • Low-dose vaginal estrogen therapy improves sexual function in postmenopausal women with genitourinary syndrome of menopause. • Nonestrogen alternatives FDA approved for dyspareunia include ospemifene and intravaginal DHEA. <u>Primary ovarian insufficiency</u> • Women with primary ovarian insufficiency and premature or early menopause may be at increased risk for fracture, CVD, heart failure, DM, overall mortality,

Clinical Guideline	Recommendation(s)
	persistent vasomotor symptoms, loss of fertility, bone loss, genitourinary symptoms, sexual dysfunction, cognitive and mood changes, increased risk of dementia, open-angle glaucoma, depression, and poor quality of life. • In the absence of contraindications, hormone therapy is recommended at least until the average age of menopause (approximately age 52 y), with an option for use of oral contraceptives in healthy younger women. • Results of the Women's Health Initiative trials in older women do not apply to women with primary ovarian insufficiency or premature or early menopause. • In women with BO before the average age of menopause, early initiation of estrogen therapy, with endometrial protection if the uterus is preserved, reduces vasomotor symptoms, genitourinary symptoms, risk for osteoporosis and related fractures, and likely CVD and overall mortality, with benefit seen in observational studies for CV mortality and cognitive impairment or dementia. • Fertility preservation and counseling should be explored for young women at risk for primary ovarian insufficiency. • Ovarian conservation is recommended when hysterectomy is performed for benign indications in premenopausal women at average risk for ovarian cancer. <u>Osteoporosis</u> • Hormone therapy prevents bone loss in healthy postmenopausal women, with dose-related effects on bone density. • Hormone therapy reduces fracture risk in healthy postmenopausal women. • Discontinuing hormone therapy results in rapid bone loss; however, no excess in fractures was seen in the Women's Health Initiative after discontinuation. • Hormone therapy is FDA approved for prevention of bone loss, but not for treatment of osteoporosis. • In the absence of contraindications, in women aged younger than 60 years or within 10 years of menopause onset, systemic hormone therapy is an appropriate therapy to protect against bone loss. • Unless contraindicated, women with premature menopause without prior fragility fracture or osteoporosis are best served with hormone therapy or oral contraceptives to prevent bone density loss and reduce fracture risk, rather than other bone-specific treatments, until the average age of menopause, when treatment may be reassessed. • Decisions regarding initiation and discontinuation of hormone therapy should be made primarily on the basis of extraskeletal benefits (i.e., reduction of vasomotor symptoms) and risks. <u>Cardiovascular disease and all-cause mortality</u> • For healthy symptomatic women aged younger than 60 years or within 10 years of menopause onset, the favorable effects of hormone therapy on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke. • Hormone therapy is not government approved for primary or secondary cardioprotection. (Level I) • Personal and familial risk of CVD, stroke, VTE, and breast cancer should be considered when initiating hormone therapy. • The effects of hormone therapy on CHD may vary depending on when hormone therapy is initiated in relation to a woman's age or time since menopause onset. • Initiation of hormone therapy in recently postmenopausal women reduced or had no effect on subclinical atherosclerosis progression and coronary artery calcification in randomized, controlled trials. • Observational data and meta-analyses show reduced risk of CHD in women who initiate hormone therapy when aged younger than 60 years or within 10 years of menopause onset. Meta-analyses show a null effect of hormone therapy on CHD

Clinical Guideline	Recommendation(s)
	after excluding open-label trials. • Women who initiate hormone therapy aged older than 60 years or more than 10 or 20 years from menopause onset are at higher absolute risks of CHD, VTE, and stroke than women initiating hormone therapy in early menopause. <u>Breast cancer</u> • The risk of breast cancer related to hormone therapy use is low, with estimates indicating a rare occurrence (less than one additional case per 1,000 women per year of hormone therapy use or three additional cases per 1,000 women when used for 5 years with conjugated equine estrogens [CEE] plus medroxyprogesterone acetate). • Women should be counseled about the risk of breast cancer with hormone therapy, putting the data into perspective, with risk similar to that of modifiable risk factors such as two daily alcoholic beverages, obesity, and low physical activity. • The effect of hormone therapy on breast cancer risk may depend on the type of hormone therapy, duration of use, regimen, prior exposure, and individual characteristics. • Different hormone therapy regimens may be associated with increased breast density, which may obscure mammographic interpretation, leading to more mammograms or more breast biopsies and a potential delay in breast cancer diagnosis. • A preponderance of data does not show an additive effect of underlying breast cancer risk (age, family history of breast cancer, genetic risk of breast cancer, benign breast disease, personal breast cancer risk factors) and hormone therapy use on breast cancer incidence. • Insufficient data are available to assess the risk of breast cancer with newer therapies such as tissue-selective estrogen complexes, including bazedoxifene plus CEE. • Observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women at high risk because of a family history of breast cancer or after bilateral salpingo-oophorectomy (BSO) for BRCA 1 or 2 genetic variants. • Systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe vasomotor symptoms unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists. • For survivors of breast cancer with genitourinary syndrome of menopause, low-dose vaginal estrogen therapy or DHEA may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal estrogen therapy for women on AIs. • Regular breast cancer surveillance is advised for all postmenopausal women per current breast cancer screening guidelines, including those who use hormone therapy. <u>Endometrial cancer</u> • Unopposed systemic estrogen therapy in a postmenopausal woman with an intact uterus increases the risk of endometrial cancer, so adequate progestogen is recommended. • Low-dose vaginal estrogen therapy does not appear to increase endometrial cancer risk, although trials with endometrial biopsy end points are limited to 1 year in duration. • Use of hormone therapy is an option for the treatment of bothersome menopause symptoms in women with surgically treated, early stage, low-grade endometrial

Clinical Guideline	Recommendation(s)
	cancer in consultation with a woman's oncologist if nonhormone therapies are ineffective. • Systemic hormone therapy is not advised with high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas. <u>Ovarian cancer</u> • Use of oral contraceptives is associated with a significant reduction in ovarian cancer risk. • Current and recent use of hormone therapy is associated with a small but statistically significant risk of ovarian cancer in observational studies, principally for serous type, although there was no increase in ovarian cancer risk in women randomized to EPT in the Women's Health Initiative. • In women with a history of ovarian cancer, benefits of hormone therapy use generally outweighs risks, especially with bothersome vasomotor symptoms or early menopause; use of hormone therapy is not advised in women with hormone-dependent ovarian cancers, including granulosa-cell tumors and low-grade serous carcinoma. • Short-term hormone therapy use appears safe in women with BRCA1 and BRCA2 genetic variants who undergo risk-reducing BSO before the average age of menopause. <u>Colorectal cancer</u> • Observational studies suggest a reduced incidence of colorectal cancer in current hormone therapy users, with reduced mortality. • In the Women's Health Initiative, EPT, but not estrogen therapy alone, reduced colorectal cancer risk, although cancers diagnosed in EPT users were diagnosed at a more advanced stage. There was no difference in colorectal cancer mortality with either EPT or estrogen therapy. <u>Duration of use, initiation after age 60 years, and discontinuation of hormone therapy</u> • The safety profile of hormone therapy is most favorable when initiated in healthy women aged younger than 60 years or within 10 years of menopause onset, so initiation of hormone therapy by menopausal women aged older than 60 years requires careful consideration of individual benefits and risks. • Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of CVD and breast cancer with persistent vasomotor symptoms or at elevated risk of fracture for whom other therapies are not appropriate. • Factors that should be considered include severity of symptoms, effectiveness of alternative nonhormone interventions, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer. • Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years. • Mitigation of risk through use of the lowest effective dose and potentially with a nonoral route of administration becomes increasingly important as women age and with longer duration of therapy. • Longer durations or extended use beyond age 65 should include periodic reevaluation of comorbidities with consideration of periodic trials of lowering or discontinuing hormone therapy. • For women with genitourinary syndrome of menopause, low-dose vaginal estrogen therapy may be considered for use at any age and for extended duration, if needed. • In the absence of contraindications, a woman should determine her preferred hormone therapy formulation, dose, and duration of use, with ongoing

Clinical Guideline	Recommendation(s)
	assessment and shared decision-making with her healthcare professional.

North American Menopause Society: **The 2023 Nonhormone Therapy Position Statement (2023)**[11]	Hormonal therapy remains the most effective treatment and should be considered in menopausal women aged younger than 60 years, within 10 years of their final menstrual periods, and without contraindications.
	
	Recommended Nonhormone Options for Vasomotor Symptoms (Level I: Good and consistent scientific evidence; Level II: Limited or inconsistent scientific evidence; Level III: Consensus and expert opinion)
	• Level I:
	  ○ Cognitive-behavioral therapy
	  ○ Clinical hypnosis
	  ○ SSRIs/SNRIs (paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, duloxetine)
	  ○ Gabapentin
	  ○ Fezolinetant
	• Level I-II:
	  ○ Oxybutynin
	• Level II-III:
	  ○ Weight loss
	  ○ Stellate ganglion block
	
	Among the available prescription therapies, pregabalin, clonidine, and suvorexant are not recommended for vasomotor symptoms (pregabalin level III, clonidine level I-III, suvorexant level II).

European Menopause and Andropause Society: **Maintaining post-reproductive health: A care pathway (2016)**[12]	Menopausal hormone therapy (MHT) general considerations • 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. The main benefits of MHT • 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. • 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. The main risks of MHT

Clinical Guideline	Recommendation(s)
	• 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.
Bone Health and Osteoporosis Foundation: **Clinician's Guide to Prevention and Treatment of Osteoporosis (2022)[13]**	<u>Universal recommendations for all patients</u> • Counsel individual patients on their risk for osteoporosis, fractures, and potential consequences of fractures (functional deterioration, loss of independence, increased mortality). • Recommend a diet with adequate total calcium intake (1000 mg/day for men aged 50 to 70 years; 1200 mg/day for women ≥ 51 years and men ≥ 71 years), incorporating calcium supplements if intake is insufficient. • Monitor serum 25-hydroxyvitamin D levels. • Maintain serum vitamin D sufficiency (≥ 30 ng/mL but below ≤ 50 ng/mL). Prescribe supplemental vitamin D (800 to 1000 units/day) as needed for individuals aged 50 years and older to achieve a sufficient vitamin D level. Higher doses may be necessary in some adults, especially those with malabsorption. (Note: in healthy individuals a serum 25(OH) vitamin D level ≥ 20 ng/mL may be sufficient, but in the setting of known or suspected metabolic bone disease ≥ 30 ng/mL is appropriate.) • Identify and address modifiable risk factors associated with falls, such as sedating medications, polypharmacy, hypotension, gait or vision disorders, and out-of-date prescription glasses. • Provide guidance for smoking cessation, and avoidance of excessive alcohol intake; refer for care as appropriate. • Counsel or refer patients for instruction on balance training, muscle-strengthening exercise, and safe movement strategies to prevent fracture(s) in activities of daily life. • In community-dwelling patients, refer for at-home fall hazard evaluation and remediation. • In post-fracture patients who are experiencing pain, prescribe over-the-counter analgesia, heat/ice home care, limited bed rest, physical therapy, and alternative non-pharmacologic therapies when appropriate. In cases of intractable or chronic pain, refer to a pain specialist or physiatrist. • Coordinate post-fracture patient care via fracture liaison service (FLS) and multidisciplinary programs in which patients with recent fractures are referred for osteoporosis evaluation and treatment, rehabilitation, and transition management. <u>Pharmacologic treatment recommendations</u> • No uniform recommendation applies to all patients. Management plans must be individualized. • Current FDA-approved pharmacologic options for osteoporosis are as follows: o Bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid) o Estrogen-related therapy (ET/HT, raloxifene conjugated estrogens/ bazedoxifene) o Parathyroid hormone analogs (teriparatide, abaloparatide)

Clinical Guideline	Recommendation(s)
	○ RANK-ligand inhibitor (denosumab) ○ Sclerostin inhibitor (romosozumab) ○ Calcitonin salmon • Consider initiating pharmacologic treatment in postmenopausal women and men ≥ 50 years of age who have the following: ○ Primary fracture prevention: ▪ T-score ≤ − 2.5 at the femoral neck, total hip, lumbar spine, 33% radius (some uncertainty with existing data) by DXA. ▪ Low bone mass (osteopenia: T-score between − 1.0 and − 2.5) at the femoral neck or total hip by DXA with a 10-year hip fracture risk ≥ 3% or a 10-year major osteoporosis-related fracture risk ≥ 20% (i.e., clinical vertebral, hip, forearm, or proximal humerus) based on the US-adapted FRAX® model. ○ Secondary fracture prevention: ▪ Fracture of the hip or vertebra regardless of BMD. ▪ Fracture of proximal humerus, pelvis, or distal forearm in persons with low bone mass (osteopenia: T-score between − 1.0 and − 2.5). The decision to treat should be individualized in persons with a fracture of the proximal humerus, pelvis, or distal forearm who do not have osteopenia or low BMD. • Initiate antiresorptive therapy following discontinuation of denosumab, teriparatide, abaloparatide, or romosozumab.
North American Menopause Society: **The 2020 Genitourinary Syndrome of Menopause Position Statement (2020)[14]**	• Education about and screening for genitourinary syndrome of menopause (GSM) is recommended for perimenopausal and postmenopausal women. • GSM describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract, including the vagina, labia, urethra, and bladder. This syndrome includes genital symptoms of dryness, burning, and irritation; urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs); and sexual symptoms of pain and dryness. • First-line therapies for women with GSM include nonhormone lubricants with sexual activity and regular use of long-acting vaginal moisturizers. • For women with moderate to severe GSM and those who do not respond to lubricants and moisturizers, several safe and effective options are available: ○ Low-dose vaginal estrogen therapy (ET) ○ Vaginal dehydroepiandrosterone (DHEA) ○ Ospemifene ○ Systemic ET (when vasomotor symptoms (VMS) are also present) • For women with a history of breast or endometrial cancer, management depends on a woman's preferences, symptom severity, and understanding of potential risks after consultation with her oncologist. • Although product labeling for low-dose vaginal ET notes risks associated with systemic hormone therapy (including CHD, stroke, VTE, breast and endometrial cancer), these risks are highly unlikely given minimal systemic absorption and reassuring findings from clinical trials and observational studies. • Use of a progestogen is not recommended with low-dose vaginal ET, although women at increased risk of endometrial cancer may warrant endometrial surveillance. Endometrial safety clinical trial data are not available for use longer than 1 year, although observational studies are reassuring regarding longer-term use. • Routine endometrial surveillance is not recommended for asymptomatic women using low dose vaginal ET. Transvaginal ultrasound or intermittent progestogen therapy may be considered for women at increased risk of endometrial cancer. • Spotting or bleeding in a postmenopausal woman requires a thorough evaluation that may include transvaginal ultrasound (TVU) and/or endometrial biopsy. • Energy-based therapies, including vaginal laser and radiofrequency devices,

Clinical Guideline	Recommendation(s)
	require long-term, sham-controlled safety and efficacy studies before their routine use can be recommended. • Therapy for GSM should be continued, with appropriate clinical follow up, for as long as bothersome symptoms are present.
American College of Cardiology: **Updated Recommendations for Primary Prevention of CVD in Women (2020)**[15]	• CVD continues to be the leading cause of morbidity and mortality among women. • Unique risk factors related to female sex include pregnancy-associated conditions such as hypertensive disorders of pregnancy, gestational diabetes mellitus, preterm birth, and pregnancy loss. Intrauterine growth restriction has also been associated with increased risk for dyslipidemia, insulin resistance, and diastolic dysfunction. • When added to current risk prediction models, pregnancy-related conditions (such as gestational diabetes) do not increase the accuracy of such models. This may be due to the association of pregnancy-related risk factors associated with traditional risk factors, which are incorporated into current prediction models. However, identification of such pregnancy-related conditions may help identify younger women (with low risk scores) to allow for earlier monitoring of cardiometabolic factors and management as needed earlier in a woman's life. • Premature menopause, defined as menopause before the age of 40 years, is associated with increased risk for CVD. In the 2018 cholesterol guidelines, premature menopause was included as a risk-enhancing factor. • Polycystic ovarian syndrome (POS) is associated with cardiometabolic factors, which, in turn, are associated with increased CVD risk. These POS factors include abdominal obesity, abnormal glucose control and diabetes, elevated blood pressure, and dyslipidemia. • Sex-related differences in traditional risk factors are prevalent. Hypertension is highly prevalent among women, in particular non-Hispanic black women, compared to other groups. Obesity is a strong risk factor for hypertension among women. Sodium restriction among postmenopausal women with hypertension may be particularly beneficial. Diabetes is also a particularly strong risk factor for CVD and heart failure among women. • Sex-related differences in CV medications exist. For women of childbearing years, modification of medications typically used for management of CVD and related risk factors may be needed. This includes the use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers or statins, which are not recommended if pregnancy is planned or occurs. For many women with CV risk factors or CVD, receipt of evidence-based medications is often less likely to occur compared to men with similar risk factors or CV conditions. Last, differences in the efficacy of medications may differ by sex. • Women are at greater risk for stroke in the setting of atrial fibrillation compared to men. Guidelines also recommend novel anticoagulants for women as the first choice for anticoagulation, given the evidence of lower risk of bleeding in women taking a novel agent as compared to vitamin K antagonists. The 2019 guidelines were revised to recommend anticoagulation for women with a CHA2DS2-VASc score of ≥3 (prior recommendations were for ≥2). • There are no recommendations for the use of menopausal hormonal therapy for CV prevention at this time. Long-standing evidence suggests either no benefit or increased risk for women when hormonal therapy is used. However, researchers have and continue to investigate the potential for a "timing hypothesis" where hormonal therapy may be of benefit (related to CV risk) among women closer to the time of menopausal onset. Providers are recommended to review each woman's risk factor profile and provide a tailored and shared decision-making discussion when menopausal hormonal therapy is considered, even among younger perimenopausal women. • Psychosocial factors such as depression, anxiety, and acute or chronic emotional

Clinical Guideline	Recommendation(s)
	stress are often observed to be more prevalent among women compared to men. Given the association between these factors and CVD risk, providers are recommended to identify and assist in the management of such factors as part of CVD prevention.
International Menopause Society: **Updated 2013 Recommendations on women's midlife health and menopause hormone therapy (2016)[16]**	• 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. • 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.
American Association	Who Needs Pharmacologic Therapy?

Clinical Guideline	Recommendation(s)
of Clinical Endocrinologists: **Clinical Practice Guideline for the Diagnosis and Treatment of Postmenopausal Osteoporosis (2020)**[17]	• Pharmacologic therapy is strongly recommended for patients with osteopenia or low bone mass and a history of fragility fracture of the hip or spine. • Pharmacologic therapy is strongly recommended for patients with a T-score of − 2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius. • Pharmacologic therapy is strongly recommended for patients with a T-score between − 1.0 and − 2.5 if the FRAX® (fracture risk assessment tool) (or if available, trabecular bone score [TBS]-adjusted FRAX®) 10-year probability for major osteoporotic fracture is ≥ 20% or the 10-year probability of hip fracture is ≥ 3% in the U.S. or above the country-specific threshold in other countries or regions. • Consider patients with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than − 3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture > 30%, hip fracture > 4.5%) or other validated fracture risk algorithm to be at very high fracture risk. Consider patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, to be high risk. <u>What Medication Should Be Used to Treat Osteoporosis?</u> • Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, denosumab, risedronate, and zoledronate are appropriate as initial therapy for most osteoporotic patients with high fracture risk. • Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronate should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk. • Ibandronate or raloxifene may be appropriate initial therapy in some cases for patients requiring drugs with spine-specific efficacy. <u>How Long Should Patients Be Treated?</u> • Limit treatment with abaloparatide and teriparatide to two years and follow abaloparatide or teriparatide therapy with a bisphosphonate or denosumab. • Limit treatment with romosozumab to one year and follow with a drug intended for long-term use, such as a bisphosphonate or denosumab). • For oral bisphosphonates, consider a bisphosphonate holiday after five years of treatment if fracture risk is no longer high (such as when the T score is greater than -2.5, or the patient has remained fracture free), but continue treatment up to an additional five years if fracture risk remains high. • For oral bisphosphonates, consider a bisphosphonate holiday after six to 10 years of stability in patients with very high fracture risk. • For zoledronate, consider a bisphosphonate holiday after three years in high-risk patients or until fracture risk is no longer high, and continue for up to six years in very-high-risk patients. • The ending of a bisphosphonate holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in bone mineral density beyond the least significant change (LSC) of the dual-energy X-ray absorptiometry (DXA) machine, or an increase in bone turnover markers. • A holiday is not recommended for non-bisphosphonate antiresorptive drugs, and treatment with such agents should be continued for as long as clinically appropriate. • If denosumab therapy is discontinued, patients should be transitioned to another antiresorptive. <u>What Is the Role of Concomitant Use of Therapeutic Agents?</u>

Clinical Guideline	Recommendation(s)
	• Until the effect of combination therapy on fracture risk is better understood, AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis. <u>What Is the Role of Sequential Use of Therapeutic Agents?</u> • Follow treatment with an anabolic agent (e.g., abaloparatide, romosozumab, teriparatide) with a bisphosphonate or denosumab to prevent bone density decline and loss of fracture efficacy.
United States Preventive Services Task Force: **Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons (2022)**[18]	• This recommendation statement applies to asymptomatic, postmenopausal persons who are considering hormone therapy for the primary prevention of chronic medical conditions. It does not apply to persons who are considering hormone therapy for the management of perimenopausal symptoms, such as hot flashes or vaginal dryness. It also does not apply to persons who have had premature menopause (primary ovarian insufficiency) or surgical menopause. • The use of combined estrogen and progestin has no net benefit for the primary prevention of chronic conditions in most postmenopausal persons with an intact uterus. • The use of estrogen alone has no net benefit for the primary prevention of chronic conditions in most postmenopausal persons who have had a hysterectomy. • Benefits of preventative medicine o Use of combined estrogen and progestin has a moderate benefit in reducing the risk of fractures in postmenopausal persons, adequate evidence that it has a small benefit in reducing the risk of diabetes and colorectal cancer, and adequate evidence that it does not have a beneficial effect on risk of coronary heart disease. o The use of estrogen without progestin has generally been restricted to persons who have had a hysterectomy, because unopposed estrogen use increases the risk of endometrial cancer in persons with an intact uterus. o Use of estrogen alone has a moderate benefit in reducing the incidence of fractures in postmenopausal persons. There is adequate evidence that the use of estrogen alone has a moderate benefit in reducing the risk of developing or dying of invasive breast cancer and a small benefit in reducing the risk of diabetes. There is adequate evidence that estrogen use does not have a beneficial effect on risk of coronary heart disease. • Harms of preventative medicine o Use of combined estrogen and progestin is associated with moderate harms, including increased risk of invasive breast cancer, stroke, venous thromboembolism, dementia, gallbladder disease, and urinary incontinence. o There is adequate evidence that use of estrogen alone is associated with moderate harms, including increased risk of stroke, venous thromboembolism, gallbladder disease, and urinary incontinence.

III. Indications

The Food and Drug Administration (FDA)-approved indications 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[1-3]

Indications	Fezolinetant
Treatment of moderate to severe vasomotor symptoms due to menopause	✔

IV. Pharmacokinetics

The pharmacokinetic parameters are listed in Table 4.

Table 4. Pharmacokinetic Parameters[1]

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
Fezolinetant	Not reported	51%	Primary: CYP1A2 Metabolite: ES259564 20-fold less potent than parent	76.9% urine 14.7% feces	9.6 hours

V. Drug Interactions

Major drug interactions are listed in Table 5.

Table 5. Major Drug Interactions[3]

Generic Name(s)	Interaction	Mechanism
Fezolinetant	CYP1A2 inhibitors	Fezolinetant is contraindicated in individuals using CYP1A2 inhibitors. Fezolinetant is a substrate of CYP1A2. Concomitant use of fezolinetant with drugs that are weak, moderate, or strong CYP1A2 inhibitors, increase the plasma C_{max} and AUC of fezolinetant.

VI. Adverse Drug Events

The most common adverse drug events reported are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported[2,3]

Adverse Event	Fezolinetant
Abdominal pain*	4.3%
Diarrhea	3.9%
Insomnia	3.9%
Back pain	3.0%
Hot flush	2.5%
Hepatic transaminase elevation†	2.3%

*Abdominal pain (including Abdominal pain, Abdominal pain lower, Abdominal pain upper)
†Hepatic transaminase elevations (including Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased)

VII. Dosing and Administration

The usual dosing regimens are listed in Table 7.

Table 7. Usual Dosing Regimens[1-3]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Fezolinetant	Treatment of moderate to severe vasomotor symptoms associated with menopause: Tablet: 45 mg daily	Safety and efficacy in children have not been established.	Tablet: 45 mg

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lederman et al.[19] (2023) SKYLIGHT 1 Fezolinetant 30 mg daily vs fezolinetant 45 mg daily vs placebo	DB, MC, PC, RCT Women 40 to 65 years of age with an average of seven or more moderate-to-severe hot flashes per day	N=527 12 weeks	Primary: Mean change in frequency and severity of vasomotor symptoms from baseline to weeks four and 12 (via electronic hot flash diary) Secondary: Mean change in the total score in Patient-Reported Outcomes Measurement Information System Sleep Disturbance—Short Form 8b (PROMIS SD SF 8b) from baseline to week 12; safety	Primary: Compared with placebo, fezolinetant 30 mg and fezolinetant 45 mg reduced the frequency of vasomotor symptoms at week four (difference in change in least squares mean -1.87 [SE, 0.42; P<0.001], -2.07 [SE, 0.42; P<0.001]) and week 12 (-2.39 [SE, 0.44; P<0.001], -2.55 [SE, 0.43; P<0.001]). Compared with placebo, fezolinetant 30 mg and 45 mg reduced the severity of vasomotor symptoms at week four (-0.15 [0.06; P=0.012], -0.19 [0.06; P=0.002]) and week 12 (-0.24 [0.08; P=0.002], -0.20 [0.08; P=0.007]). Secondary: For the key secondary endpoint, the observed improvements in patient-reported sleep disturbance for fezolinetant 30 mg and 45 mg versus placebo were not significant at week 12. During the first 12 weeks, treatment-emergent adverse events occurred in 65 (37%) of 174 women in the fezolinetant 30 mg group, 75 (43%) of 173 in the fezolinetant 45 mg group, and 78 (45%) of 175 in the placebo group. The incidence of liver enzyme elevations was low (placebo n=1; fezolinetant 30 mg n=2; fezolinetant 45 mg n=0) and these events were generally asymptomatic, transient, and resolved while on treatment or after treatment discontinuation.
Johnson et al.[20] (2023) SKYLIGHT 2 Fezolinetant 30 mg daily vs	ES Completers of SKYLIGHT 1 were rerandomized	N=484 40 week extension	Primary: Extension efficacy as shown by change in VMS frequency and severity Secondary:	Primary: Persistence of efficacy for all fezolinetant groups was observed during the 40-week active treatment extension period. Secondary: No new safety signals were observed in the 40-week active treatment extension period that were not evident in the 12-week placebo-controlled period. Serious treatment-emergent adverse events were infrequent,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fezolinetant 45 mg daily			Extension safety	reported by 2%, 1%, and 0% of those receiving fezolinetant 30 mg, fezolinetant 45 mg, and placebo, respectively.
Neal-Perry et al.[21] (2023) SKYLIGHT 4 Fezolinetant 30 mg daily vs fezolinetant 45 mg daily vs placebo	DB, MC, RCT Postmenopausal women seeking treatment for vasomotor symptoms associated with menopause	N=1,830 52 weeks	Primary: Treatment-emergent adverse events, percentage of participants with endometrial hyperplasia, and percentage with endometrial malignancy Secondary: Change in bone mineral density (BMD) and trabecular bone score	Primary: Treatment-emergent adverse events occurred in 64.1% of the placebo group, 67.9% of the fezolinetant 30-mg group, and 63.9% of the fezolinetant 45-mg group. Treatment-emergent adverse events leading to discontinuation were similar across groups (placebo, 4.3%; fezolinetant 30 mg, 5.6%; fezolinetant 45 mg, 4.6%). Endometrial safety was assessed in 599 participants. In the fezolinetant 45-mg group, 1 of 203 participants had endometrial hyperplasia (0.5%; upper limit of one-sided 95% CI, 2.3%); there were no cases in the placebo (0/186) or fezolinetant 30 mg (0/210) group. Endometrial malignancy occurred in 1 of 210 in the fezolinetant 30-mg group (0.5%; 95% CI, 2.2%) with no cases in the other groups. Secondary: Changes in BMD and trabecular bone score were similar across groups.

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,
Miscellaneous abbreviations: BMD=bone mineral density, BP=blood pressure, CI=confidence interval, HR=hazard ratio, OR=odds ratio

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Fezolinetant	tablet	Veozah®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

Veozah® (fezolinetant) was approved in 2023 for the treatment of moderate to severe vasomotor symptoms due to menopause.[1-3] The SKYLIGHT 1 and 2 trials demonstrated fezolinetant's superiority over placebo in significantly reducing the frequency and severity of hot flashes over 24 hours. Fezolinetant was generally well tolerated in clinical trials, with adverse effects most notable for elevated hepatic transaminases that were generally asymptomatic.[19-21] The prescribing information for fezolinetant includes a warning for elevated hepatic transaminases. Patients need baseline bloodwork before starting the medication, and routine bloodwork needs to be done every three months for the first nine months of using the medication. Fezolinetant is contraindicated in cirrhosis, severe renal impairment/end-stage renal disease, and concomitant use with CYP1A2 inhibitors.[3] The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society lists fezolinetant with a level I recommendation for pharmacotherapy alongside SSRIs/SNRIs and gabapentin.[11] According to those guidelines, hormonal therapy remains the most effective treatment and should be considered in menopausal women aged younger than 60 years, within 10 years of their final menstrual periods, and without contraindications.[11]

There is insufficient evidence to support that brand fezolinetant is safer or more efficacious than other agents 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 fezolinetant 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.

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