Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Central α-Agonists
Single Entity Agents
AHFS Class 240816
September 10, 2008

I. Overview

Drugs to treat hypertension are among the most frequently prescribed pharmacologic agents. The incidence of hypertension increases with age, so the proper selection of antihypertensive drugs is taking on increasing importance in the United States (US) due to increased longevity as well as rising rates of obesity.[1,2] While a multitude of neurohormonal, renal, and vascular mechanisms have been proposed as contributors to hypertension, no specific cause can be assigned in most cases.[3,4] Antihypertensive agents are separated into broad classes depending upon which aspect of blood pressure regulation they affect: sodium and water balance, the sympathetic nervous system, resistance from vascular smooth muscle, or the renin-angiotensin-aldosterone system (RAAS).[5] Most patients will require therapy with more than one antihypertensive drug to achieve adequate blood pressure control, and in these cases, the selection of agents from more than one class is usually advised.[1,5]

The autonomic nervous system influences blood pressure through its effects on heart rate, contractile force, venous tone, and peripheral vascular resistance.[6,7] Catecholamines serve as important transmitters of these messages, and the primary classification of adrenergic receptors (α and β) was made by measuring their sensitivity to certain catecholamines including epinephrine, norepinephrine, and isoproterenol.[7,8] Subtypes of these receptors (α_1, α_2, β_1, β_2, β_3) are distributed in the body among various tissues and organs.[7,8] Several classes of pharmacological agents to be discussed in these reviews work through their effects, more or less selective, upon these receptor subtypes.

Central α-agonists lower blood pressure primarily through stimulation of α_2-adrenergic receptors in the central nervous system (CNS).[3,9] This action inhibits sympathetic vasomotor centers, causing decreased sympathetic outflow from the CNS and an associated increase in vagal tone. Sympathetic activity is reduced while parasympathetic activity is increased, and this leads to reductions in total peripheral resistance, systolic and diastolic blood pressure, baroreceptor reflexes, heart rate, and cardiac output.[3,9] Plasma renin activity is also affected by central α-agonists, but the relationship between this and the hypotensive effect of these agents has not been fully elucidated.[9] Chronic central α-agonist use is associated with sodium and fluid retention, which may require concomitant diuretic therapy.[3]

The single entity central α-agonists included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available generically with the exception of the clonidine transdermal patch. Methyldopate, the ethyl ester of methyldopa, is administered primarily on an inpatient basis in institutions.[10] Since it is not routinely dispensed in an outpatient pharmacy, it has not been included in this review.

Table 1. Single Entity Central α-Agonists Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
clonidine	tablet, transdermal patch	Catapres®*, Catapres-TTS®	clonidine
guanabenz	tablet	Wytensin®*†	guanabenz
guanfacine	tablet	Tenex®*	guanfacine
methyldopa	tablet	Aldomet®*†	methyldopa
methyldopate^	injection	none	none

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
^Product is primarily administered in an institution.

II. Evidence-Based Medicine and Current Treatment Guidelines

The consensus of various national and international treatment guidelines is that pharmacotherapy be tailored according to blood pressure goals with consideration given to cardiovascular risk factors. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends thiazide diuretics as first-line therapy for patients with uncomplicated hypertension.[1] Central α-agonists are not considered first-line therapy for hypertension due to their relatively high incidence of side effects.[11] Methyldopa is considered a drug of choice for the treatment of chronic hypertension during pregnancy based on long-term follow up studies supporting safety in the fetus.[1]

Table 2 outlines the current national and international treatment guidelines for the pharmacologic management of hypertension. For a more comprehensive overview of the pharmacologic management of this condition, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Single Entity Central α-Agonists

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)[1]**	• Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)[12]**	• The use of central α-agonists was not addressed in this guideline.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)[13]**	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], calcium channel blocking agents [CCBs]), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous myocardial infarction (MI) (ACE inhibitors, β-blocking agents [β-blockers], ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics).
Treatment Guidelines From the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)[14]**	• The use of central α-agonists was not addressed in this guideline.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care:**	• The use of central α-agonists was not addressed in this guideline.

Clinical Guideline	Recommendation(s)
Pharmacological Update (2006)[15]	
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008[16]**	• The use of central α-agonists was not addressed in this guideline.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)[17]**	• The use of central α-agonists was not addressed in this guideline.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)[11]**	• The use of central α-agonists was not addressed in this guideline.

III. Indications

Table 3 summarizes the Food and Drug Administration (FDA)-approved indications for the single entity central α-agonists. 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 Single Entity Central α-Agonists[5,6]

Indication	Clonidine	Guanabenz	Guanfacine	Methyldopa
Hypertension	✔ *	✔ †	✔ *	✔

*Alone or in combination with other antihypertensive agents.
†Alone or in combination with a thiazide diuretic.

IV. Pharmacokinetics

Table 4 includes the pharmacokinetic properties for the single entity central α-agonists.

Table 4. Pharmacokinetic Parameters of the Single Entity Central α-Agonists[18-23]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination (%)	Half-Life (hours)
Clonidine, oral	75-100	20-40	Liver	None	40-60	Urine (40-60) Feces (22)	12-16
Clonidine, transdermal	60	20-40	Liver	None	40-60	Urine (40-60) Feces (22)	6-20
Guanabenz	75	90	Unknown	None	<1	Feces (16)	6
Guanfacine	80	70	Liver	None	40-75	Urine (40-75)	17
Methyldopa	25-50	<15	Liver	α-methyldopa-mono-*o*-sulfate	70	Urine (45) Feces (30-50)	1.7

V. Drug Interactions

Clinically significant drug interactions for the single entity central α-agonists are listed in Table 5.

Table 5. Significant Drug-Drug Interactions for the Single Entity Central α-Agonists[24]

Drug	Significance Level	Interaction	Mechanism
Clonidine	1	β-blockers (acebutolol, atenolol, betaxolol, carteolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol)	Concomitant use of clonidine and a β-blocker may attenuate or reverse antihypertensive effects since β-blocker inhibition of β_2-receptor mediated vasodilation leaves peripheral α_2-receptor mediated vasoconstriction unopposed to clonidine stimulation.
Clonidine	1	Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Concomitant use of clonidine and a tricyclic antidepressant may cause loss of blood pressure control by tricyclic antidepressant inhibition of central α_2-receptors.
Methyldopa	2	Sympathomimetics (dobutamine, dopamine, ephedrine, epinephrine, metaraminol, norepinephrine, phenylephrine, pseudoephedrine)	The coadministration of methyldopa and sympathomimetics may result in an increased pressor response, possibly resulting in hypertension. The mechanism is not fully understood.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

Central α-agonists are not considered first-line therapies because they are associated with a significantly greater incidence of side effects compared to other antihypertensive agents. Frequent side effects include sedation and dry mouth. Abrupt discontinuation may cause nervousness, palpitations, headache, perspiration, nausea, and agitation. In some cases, sudden discontinuation may cause potentially dangerous rebound hypertension.[9] There is a lower incidence of dry mouth and drowsiness with the clonidine patch compared with oral clonidine.[7] Conversely, the patch formulation is associated with a greater incidence of dermatological reactions, such as pruritus and rash.[7] Centrally acting agents are associated with higher rates of sexual dysfunction compared to other antihypertensive agents. Significant adverse drug events with the single entity central α-agonists are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Single Entity Central α-Agonists[18-21,23]

Adverse Event(s)	Clonidine Oral	Clonidine Transdermal*	Guanabenz	Guanfacine	Methyldopa
Cardiovascular					
Arrhythmia	-	-	<3	-	-
Atrioventricular block	<1	-	-	-	-
Bradycardia	-	-	-	≤3	<1
Chest pain	<1	-	<3	≤3	-
Congestive heart failure	<1	-		-	-
Edema	-	-	<3	-	<1
Electrocardiogram abnormalities	<1	-	-	-	-
Flushing	-	-	-	-	-
Hypotension	-	-	-	-	<1
Orthostatic hypotension	3	-	-	-	<1
Orthostasis	-	-	5	-	-
Palpitations	-	-	<3	≤3	-
Palpitations and tachycardia	<1	-	-	-	-

Adverse Event(s)	Clonidine Oral	Clonidine Transdermal*	Guanabenz	Guanfacine	Methyldopa
Peripheral edema	-	-	-	-	>10
Syncope	<1	-	-	-	<1
Tachycardia	<1	-	-	-	-
Central Nervous System					
Agitation	<1	-	-	-	-
Amnesia	-	-	-	≤3	-
Anxiety	-	-	<3	-	1-10
Ataxia	-	-	<3	-	-
Confusion	-	-	-	≤3	-
Delirium	<1	-	-	-	-
Depression	1	-	<3	≤3	1-10
Dizziness	16	2	12-17	12-15	<1
Drowsiness	33	12	39	-	1-10
Fatigue	4	6	-	2-10	-
Hallucinations	<1	-	-	-	-
Headache	1	5	5	3-13	1-10
Insomnia	5	2	-	≤3	-
Lethargy	-	3	-	-	-
Nervousness	3	1	-	-	-
Sedation	10	3	-	-	-
Sleep disturbances	-	-	<3	-	-
Somnolence	-	-	20-50	5-39	-
Weakness	10	-	10	2-7	-
Dermatological					
Allergic contact sensitization	-	5	-	-	-
Alopecia	<1	-	-	-	-
Angioedema	<1	-	-	-	-
Blanching	-	1	-	-	-
Burning	-	3	-	-	-
Contact dermatitis	-	19	-	-	-
Dermatitis	-	-	-	≤3	-
Edema	3	3	-	-	-
Erythema	-	15-50	<1	-	-
Excoriation	-	3	-	-	-
Exfoliative dermatitis	-	-	-	-	<1
Hives	<1	-	-	-	-
Hyperpigmentation	-	5	-	-	-
Hypopigmentation	-	-	-	-	-
Morbilliform or macro papular eruptions	-	1	-	-	-
Pruritus	7	15-50	<3	≤3	-
Purpura	-	-	-	≤3	-
Rash	1	-	<3	-	-
Sweating	-	-	-	≤3	<1
Throbbing	-	3	-	-	-
Urticaria	<1	<1	-	-	-
Vesiculation	-	7	-	-	-
Endocrine and Metabolic					
Gynecomastia	<1	-	<3	-	<1
Impotence	3	2	<1	3-7	-
Sexual dysfunction	3	2	-	≤3	<1
Sodium retention	-	-	-	-	<1
Gastrointestinal					

Adverse Event(s)	Clonidine Oral	Clonidine Transdermal*	Guanabenz	Guanfacine	Methyldopa
Abdominal Pain	<1	-	<3	≤3	-
Anorexia	1	-	-	-	-
Constipation	10	1	<3	2-15	-
Diarrhea	-	-	<3	≤3	-
Dry mouth	40	25	28-38	10-54	1-10
Dry throat	-	2	-	-	-
Dyspepsia	-	-	-	≤3	-
Dysphagia	-	-	-	≤3	-
Nausea	5	1	<3	≤3	-
Taste alteration	-	1	✔	≤3	-
Vomiting	5	-	<3	-	-
Weight gain	1	-	-	-	-
Genitourinary					
Micturition difficulties	1	-	-	-	-
Nocturia	1	-	-	-	-
Polyuria	-	-	<3	-	-
Testicular disorder	-	-	-	≤3	-
Urinary incontinence	-	-	-	≤3	<1
Urinary retention	1	-	-	-	-
Hematologic					
Granulocytopenia	-	-	-	-	<1
Hemolytic anemia	-	-	-	-	<1
Leukopenia	-	-	-	-	<1
Pancytopenia	-	-	-	-	-
Thrombocytopenia	<1	-	-	-	<1
Hepatic					
Cholestasis	-	-	-	-	<1
Cirrhosis	-	-	-	-	<1
Elevated liver enzyme levels	-	-	-	-	<1
Hepatitis	<1	-	-	-	<1
Jaundice	-	-	-	-	<1
Liver function test abnormalities	1	-	-	-	-
Musculoskeletal					
Hypokinesia	-	-	-	≤3	-
Leg cramps	<1	-	-	≤3	-
Myalgia	<1	-	<3	-	-
Respiratory					
Dyspnea	-	-	<3	≤3	<1
Rhinitis	-	-	-	≤3	-
Other					
Amnesia	-	-	-	-	-
Blurred vision	<1	-	3	-	-
Conjunctivitis	-	-	-	≤3	-
Drug fever	-	-	-	-	1-10
Iritis	-	-	-	≤3	-
Malaise	1	-	-	≤3	-
Nightmares	<1	-	-	-	-
Paresis	-	-	-	≤3	-
Paresthesia	-	-	-	≤3	-
Tinnitus	-	-	-	≤3	-
Vision disturbance	-	-	-	≤3	-
Withdrawal syndrome	1	-	-	-	-

*Adverse events for the oral formulation also listed in product information.
✔ Percent not specified.
-Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the single entity central α-agonists are summarized in Table 7.

Table 7. Usual Dosing For the Single Entity Central α-Agonists[18-22]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Clonidine	Hypertension: Oral: initial, 0.1 mg twice daily; maintenance, 0.1 to 0.6 mg/day in 2 divided doses; maximum, 2.4 mg/day Transdermal: initial, 0.1 mg patch once weekly; maintenance, 0.1 to 0.3 mg patch once weekly; maximum, 2 of the 0.3 mg patches once weekly	Safety and efficacy in children under 12 have not been established.	Tablet: 0.1 mg 0.2 mg 0.3 mg Transdermal patch: 0.1 mg/24 hours 0.2 mg/24 hours 0.3 mg/24 hours
Guanabenz	Hypertension: Tablet: initial, 4 mg twice daily; maintenance, 8 to 32 mg twice daily; maximum, 32 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 4 mg 8 mg
Guanfacine	Hypertension: Tablet: initial, 1 mg once daily at bedtime; maintenance, 1 to 2 mg once daily; maximum, 3 mg once daily	Safety and efficacy in children under 12 have not been established.	Tablet: 1 mg 2 mg
Methyldopa	Hypertension: Tablet: initial, 250 mg 2 to 3 times daily; maintenance, 500 to 2,000 mg daily in 2 divided doses; maximum dose, 3 g daily	Hypertension: Tablet: initial, 10 mg/kg/day in 2 to 4 divided doses, then titrate up or down until adequate response achieved; maximum, 65 mg/kg/day or 3 g daily, whichever is less	Injection (vial): 250 mg/ 5 mL Tablet: 125 mg 250 mg 500 mg

VIII. Effectiveness

There are limited comparative trials regarding the single entity central α-agonists. The available clinical trials are included in Table 8.

Table 8. Comparative Clinical Trials Using the Single Entity Central α-Agonists

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Houston et al[25] Clonidine transdermal 0.1 to 0.3 mg QD plus nifedipine 60 mg QD (single entity products) vs nifedipine 60 mg QD plus placebo	OL, prospective, PC Male and nonpregnant female patients between 18 and 75 years of age with mild to moderate hypertension and inadequate response to nifedipine	N=42 8 weeks	Primary: change in seated DBP to less than 90 mm Hg at 8 weeks Secondary: Not reported	Primary: Patients on combination therapy experienced a reduction of 16/14 mm Hg in the mean seated blood pressure vs placebo (*P*<0.01) with mean seated blood pressure of 127/87 mm Hg. A reduction of 5/10 mm Hg in the mean seated blood pressure was seen with combination therapy vs nifedipine monotherapy (*P*<0.01). A reduction of 18/12 mm Hg in the mean standing blood pressure was seen with combination therapy vs placebo (*P*<0.01). A reduction of 9/9 mm Hg in the mean standing blood pressure was seen with combination therapy vs nifedipine monotherapy (*P*<0.01). Secondary: Not reported
Kluyskens et al[26] Guanabenz mean dose 24 mg QD vs clonidine mean dose 0.45 mg QD	DB, PC Non-pregnant patients 21 to 64 years of age with mild to moderate hypertension	N=29 Duration 8 weeks	Primary: Reduction in DBP between 5 to 10 mm Hg based on patients' pretreatment values Secondary: Not reported	Primary: Both treatments resulted in statistically significant reductions in SBP and DBP from baseline and placebo periods (*P*<0.001). Secondary: Not reported
McCarron D[27] Guanabenz 16 to 31 mg QD	DB, MC, RCT Patients with mild to moderate hypertension	N=147 6 months	Primary: Change in supine DBP	Primary: Patients in both the guanabenz and hydrochlorothiazide groups demonstrated a significant decreases in supine DBP (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs HCTZ 50 to 75 mg QD			Secondary: Side effects	Secondary: Mild side effects (dry mouth, drowsiness) were reported more frequently (*P*<0.01) in the guanabenz-treated group vs the HCTZ group.
Lilja M et al[28] Oral clonidine 0.1 mg BID plus placebo patch vs transdermal clonidine 0.2 mg QD plus placebo tablets BID	DB, DD, PC, RCT, XO Patients with mild to moderate hypertension	N=16 12 weeks	Primary: Change from baseline in supine and standing SBP and heart rate Secondary: Difference in primary endpoints between oral and transdermal clonidine	Primary: Transdermal clonidine reduced both SBP and DBP by 13/7 mm Hg (*P*<0.01/0.01) and heart rate by 9 beats/min (*P*<0.01) in the supine position. Oral clonidine produced a statistically significant reduction 11 mm Hg (*P*<0.01) only in supine SBP. In a standing position, transdermal clonidine reduced SBP and DBP by 14 to 9 mm Hg (*P*<0.01/0.01) and heart rate by 9 beats/min (*P*<0.01). Oral clonidine reduced only the standing heart rate to a statistically significant extent 8 beats/min (*P*<0.05). Secondary: There were no differences reported in primary endpoints between transdermal and oral clonidine (*P* value not reported).

Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity Central α-Agonists

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
clonidine	tablet, transdermal patch	Catapres®*, Catapres-TTS®	$$$-$$$$$	$
guanabenz	tablet	Wytensin®*†	N/A	$$$
guanfacine	tablet	Tenex®*	$$$	$
methyldopa	tablet	Aldomet®*†	N/A	$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

The central α-agonists are one of the oldest Food and Drug Administration (FDA) approved drug therapies in the antihypertensive class. The mechanism of action of these agents, which is the stimulation of α_2-adrenergic receptors in the brain, affects sympathetic and parasympathetic activity with multiple effects on the cardiovascular system. They ultimately lead to a reduction in total peripheral resistance. As a result, these agents may be useful in certain patients with underlying diseases, such as chronic obstructive pulmonary disease or peripheral vascular disease, which may be worsened by other antihypertensive agents. Methyldopa remains a drug of choice for pregnant women due to its safety profile.[1] Regardless, central α-agonists are not recommended as initial therapy for hypertension primarily because of their significant side effect profiles and the potential for severe rebound hypertension upon rapid withdrawal.[29]

There are limited head-to-head trials comparing the single entity central α-agonists. Overall, the available data demonstrates comparable safety and efficacy amongst the single entity central α-agonists. Clonidine, guanabenz, guanfacine and methyldopa are all available in oral generic formulations. The clonidine patch is not available generically. The available data fails to demonstrate enhanced efficacy of one route over another for oral and transdermal clonidine.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity central α-agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Central α-Agonists
Combination Agents
AHFS Class 240816
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I. Overview

Central α-agonists lower blood pressure primarily through stimulation of α_2-adrenergic receptors in the central nervous system (CNS).[1,2] This action inhibits sympathetic vasomotor centers, causing decreased sympathetic outflow from the CNS and an associated increase in vagal tone. Sympathetic activity is reduced while parasympathetic activity is increased, and this leads to reductions in total peripheral resistance, systolic and diastolic blood pressure, baroreceptor reflexes, heart rate, and cardiac output.[1,2] Plasma renin activity is also affected by central α-agonists, but the relationship between this and the hypotensive effect of these agents has not been fully elucidated.[2] Chronic central α-agonist use is associated with sodium and fluid retention, which may require concomitant diuretic therapy.[1]

Thiazide diuretics have been used extensively for many years in the treatment of hypertension, heart failure, and various edematous conditions. Diuretics are considered first-line treatments for patients with fluid overload associated with chronic heart failure. Diuretics provide symptomatic relief, improve cardiac function and exercise tolerance, increase sodium urinary excretion, and decrease the physical signs of fluid retention.[3] Thiazide-type diuretics are considered first-line therapy for uncomplicated hypertension. In addition, thiazides are frequently included in multidrug antihypertensive regimens in patients with comorbid conditions.

The combination central α-agonists included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Combination Central α-Agonists Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agents
clonidine and chlorthalidone	tablet	Clorpres®*, Combipres®*†	clonidine and chlorthalidone
methyldopa and hydrochlorothiazide	tablet	Aldoril-15®*†, Aldoril-25®*†, Aldoril-D30®*†, Aldoril-D50®*†	methyldopa and hydrochlorothiazide

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.

II. Evidence-Based Medicine and Current Treatment Guidelines

The general consensus of various national and international treatment guidelines is that pharmacotherapy be tailored according to blood pressure goals with consideration given to cardiovascular risk factors. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends thiazide diuretics as first-line therapy for patients with uncomplicated hypertension.[4] Central α-agonists are not considered first-line therapy for hypertension due to the relatively high incidence of side effects.[5] Methyldopa is considered a drug of choice for the treatment of chronic hypertension during pregnancy based on long-term follow up studies supporting safety in the fetus.[4]

Many patients may require more than one antihypertensive agent in order to attain blood pressure goals. The choice of additional antihypertensives is often influenced by the presence of comorbid conditions and a particular drug's side effect profile. Central α-agonists are often used in combination with diuretics. Concurrent use of these agents produces an additive antihypertensive effect, which often allows for lower doses of the individual components. Concomitant use of a diuretic and methyldopa may prevent sodium retention and increased plasma volume that may occur after prolonged methyldopa therapy.

Table 2 outlines the current national and international treatment guidelines for the pharmacologic management of hypertension. For a more comprehensive overview of the treatment of this condition, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Combination Central α-Agonists

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)[4]**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-adrenergic blocking agents (β-blockers), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium-channel blocking agents (CCBs). This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)[6]**	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).

Clinical Guideline	Recommendation(s)
	• The use of central α-agonists was not addressed in this guideline.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[7]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated.
Treatment Guidelines From the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[8]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients. • Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment. • The use of central α-agonists was not addressed in this guideline.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[9]	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • The use of central α-agonists was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[10]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2. • Multiple drug therapy is generally required to achieve blood pressure goals. • The use of central α-agonists was not addressed in this guideline.
International Society on Hypertension in Blacks:	• The use of central α-agonists was not addressed in this guideline.

Clinical Guideline	Recommendation(s)
Management of High Blood Pressure in African Americans (2003)[11]	
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)[5]**	• The use of central α-agonists was not addressed in this guideline.

III. Indications

Table 3 summarizes the Food and Drug Administration (FDA)-approved indications for the combination central α-agonists. 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 Combination Central α-Agonists[12-14]

Indication	Clonidine and Chlorthalidone	Methyldopa and Hydrochlorothiazide
Hypertension	✔ *	✔ *

*Not indicated for initial therapy of hypertension

IV. Pharmacokinetics

Table 4 includes the pharmacokinetic properties for each of the components of the combination central α-agonists.

Table 4. Pharmacokinetic Parameters of the Combination Central α-Agonists[15-21]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Clonidine	75-100	20-40	Liver	None	Urine (40-60) Feces (22)	12-16
Methyldopa	25-50	<15	Liver	α-methyldopa-mono-*o*-sulfate	Urine (45) Feces (30-50)	1.7
Chlorthalidone	65 104-116 (with PVP)	75	Not reported	None	Urine (50-74)	40-89
Hydrochloro-thiazide	50-75	40-68	Not appreciably metabolized	Not reported	Urine (>95)	6-15

PVP=povidone polyvinylpyrrolidone.

V. Drug Interactions

The combination agents share the same drug interaction profiles as their individual components. Table 5 includes the clinically significant drug-drug interactions associated with the central α-agonists and selected thiazide diuretics. **Table 5. Significant Drug-Drug Interactions for Combination Central α-Agonists[22]**

Drug	Significance Level	Interaction	Mechanism
Clonidine	1	β-blockers (acebutolol, atenolol, betaxolol, carteolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol)	Concomitant use of clonidine and a β-blocker may attenuate or reverse antihypertensive effects since β-blocker inhibition of β_2-receptor mediated vasodilation leaves peripheral α_2-receptor mediated vasoconstriction unopposed to clonidine stimulation.
Clonidine	1	Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Concomitant use of clonidine and a tricyclic antidepressant may cause loss of blood pressure control by tricyclic antidepressant inhibition of central α_2-receptors.
Chlorthalidone, hydrochloro-thiazide (HCTZ)	1	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Chlorthalidone, HCTZ	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Chlorthalidone, HCTZ	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Chlorthalidone, HCTZ	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Chlorthalidone, HCTZ	2	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Chlorthalidone, HCTZ	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate carefully in small or intermittent doses.
Chlorthalidone, HCTZ	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose

Drug	Significance Level	Interaction	Mechanism
			levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.
Methyldopa	2	Sympathomimetics (dobutamine, dopamine, ephedrine, epinephrine, metaraminol, norepinephrine, phenylephrine, pseudoephedrine)	Coadministration of methyldopa and sympathomimetics may result in an increased pressor response, possibly resulting in hypertension. The mechanism is not fully understood.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

Central α-agonists are not considered first-line therapies because they are associated with a significantly greater incidence of side effects compared to other antihypertensive agents. Frequent side effects include sedation and dry mouth. Abrupt discontinuation, may cause nervousness, palpitations, headache, perspiration, nausea, and agitation. In some cases, sudden discontinuation may cause potentially dangerous rebound hypertension. Centrally acting agents are associated with higher rates of sexual dysfunction compared to other antihypertensive agents.

Table 6 includes the adverse reactions reported with the combination central α-agonists. In general, the combination agents share the same adverse drug reaction profiles as their individual components.

Methyldopa-hydrochlorothiazide have a boxed warning regarding the use of fixed-combination products in the treatment of hypertension. This is reproduced in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Combination Entity Central α-Agonists[12-14,23]

Adverse Event	Clonidine-Chlorthalidone	Methyldopa-HCTZ
Cardiovascular		
Angina	-	✔
Atrioventricular block	<1	-
Bradycardia	-	✔
Carotid sinus sensitivity	-	✔
Chest pain	<1	-
Congestive heart failure	<1	✔
Edema	-	✔
Electrocardiogram abnormalities	<1	-
Hypotension	-	✔
Orthostatic hypotension	3	✔
Necrotizing angiitis	-	✔
Palpitations and tachycardia	<1	-
Peripheral edema	-	-
Syncope	<1	-
Tachycardia	<1	-
Central Nervous System		
Agitation	<1	-
Anxiety	-	-
Bell’s palsy	-	✔
Decreased mental acuity	-	✔
Delirium	<1	-
Depression	1	✔
Dizziness	16	✔

Adverse Event	Clonidine-Chlorthalidone	Methyldopa-HCTZ
Drowsiness	33	-
Fatigue	4	-
Hallucinations	<1	-
Headache	1	✔
Insomnia	5	-
Involuntary movements	-	✔
Light-headedness	-	✔
Nervousness	3	-
Parkinsonism	-	✔
Restlessness	-	✔
Sedation	10	✔
Vertigo	✔	-
Weakness	10	✔
Dermatological		
Alopecia	<1	✔
Angioedema	<1	-
Edema	3	-
Erythema	-	✔
Exfoliative dermatitis	-	✔
Hives	<1	-
Lupus-like syndrome	-	✔
Morbilliform or macro papular eruptions	-	✔
Photosensitivity	✔	✔
Pruritus	7	-
Purpura	✔	✔
Rash	1	✔
Stevens-Johnson syndrome	-	✔
Sweating	-	-
Throbbing	-	-
Toxic epidermal necrolysis	✔	✔
Urticaria	<1	✔
Vasculitis	✔	✔
Vesiculation	-	✔
Endocrine and Metabolic		
Blood urea nitrogen elevated	-	✔
Breast enlargement	-	✔
Electrolyte imbalance	-	✔
Gynecomastia	<1	✔
Hyperchloremic alkalosis	-	-
Hypercholesterolemia	-	-
Hyperglycemia	✔	✔
Hyperuricemia	✔	✔
Hypokalemia	-	-
Hypomagnesemia	-	-
Hyponatremia	-	-
Impotence	3	-
Pancreatitis	✔	✔
Sexual dysfunction	3	-
Sodium retention	-	-
Triglycerides increased	-	-
Gastrointestinal		

Adverse Event	Clonidine-Chlorthalidone	Methyldopa-HCTZ
Abdominal pain	<1	-
Anorexia	1	✔
Colitis	-	✔
Constipation	10	✔
Cramping	-	✔
Diarrhea	✔	✔
Distention	-	✔
Dry mouth	40	✔
Flatus	-	✔
Gastric irritation	✔	✔
Nausea	5	✔
Sialadenitis	-	✔
Sore tongue	-	✔
Taste alteration	-	-
Vomiting	5	✔
Weight gain	1	✔
Genitourinary		
Glycosuria	-	✔
Interstitial nephritis	-	✔
Micturition difficulties	1	-
Nocturia	1	-
Renal dysfunction	-	✔
Renal failure	-	✔
Urinary incontinence	-	-
Urinary retention	1	-
Hematologic		
Agranulocytosis	✔	✔
Aplastic anemia	✔	✔
Bone marrow depression	-	✔
Granulocytopenia	-	✔
Hemolytic anemia	-	✔
Leukopenia	✔	✔
Positive antinuclear antibody test	-	✔
Positive Coombs test	-	✔
Thrombocytopenia	<1	✔
Hepatic		
Cholestasis	-	-
Cirrhosis	-	-
Elevated liver enzyme levels	-	-
Hepatitis	<1	✔
Jaundice	✔	✔
Liver function test abnormalities	1	✔
Musculoskeletal		
Arthralgia	-	✔
Leg cramps	<1	-
Muscle spasm	✔	✔
Myalgia	<1	-
Weakness	-	-
Respiratory		
Dyspnea	-	✔
Pneumonitis	-	-

Adverse Event	Clonidine-Chlorthalidone	Methyldopa-HCTZ
Pulmonary edema	-	-
Respiratory distress	-	✔
Other		
Anaphylactic reactions	-	✔
Blurred vision	<1	✔
Drug fever	-	✔
Eosinophilia	-	✔
Fever	-	✔
Malaise	1	-
Myocarditis	-	✔
Nightmares	<1	✔
Paresthesia	✔	✔
Pericarditis	-	✔
Systemic lupus erythematosus	-	-
Withdrawal syndrome	1	-
Xanthopsia	✔	✔

✔ Percent not specified.
-Event not reported.

Table 7. Black Box Warning for Methyldopa-Hydrochlorothiazide[13-14]

WARNING
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

VII. Dosing and Administration

Table 8 includes the dosing and administration for each of the combination central α-agonists.

Table 8. Usual Dosing for the Combination Central α-Agonists[12-14,23]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Clonidine and chlorthalidone	Hypertension: Oral: initial, 1 tablet 0.1 mg-15 mg) 1 to 2 times daily; maintenance, 1 tablet (0.2 mg-15 mg) 1 to 2 times daily; maximum, 1 tablet (0.3 mg-15 mg) two times daily	Safety and efficacy in children have not been established.	Tablet: 0.1 mg-15 mg 0.2 mg-15 mg 0.3 mg-15 mg
Methyldopa and hydrochloro-thiazide	Hypertension: Tablet: initial, 1 tablet (250 mg-15 mg) 2 to 3 times a day or 1 tablet (250 mg-25 mg) 2 times a day; maintenance, 1 tablet (250 mg-25 mg) 2 to 3 times a day; maximum, 1 tablet (500 mg-50 mg) once daily	Safety and efficacy in children have not been established.	Tablet: 250 mg-15 mg 250 mg-25 mg 500 mg-50 mg

VIII. Effectiveness

There are limited comparative trials regarding the combination central α-agonists. The available clinical trials are included in Table 9.

Table 9. Comparative Clinical Trials Using the Combination Central α-Agonists

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Boyles et al[24] HCTZ monotherapy vs combination methyldopa 250 to 800 mg/day and HCTZ 25 to 100 mg/day Patients were initiated on HCTZ monotherapy for 2 weeks. Methyldopa was added if the patient's blood pressure failed to respond to HCTZ.	OL, RCT Patients ≥59 years with isolated systolic hypertension	N=21 18 weeks	Primary: Changes in blood pressure from baseline Secondary: Not reported	Primary: At 2 weeks standing blood pressure fell from a mean of 166/90 mm Hg at baseline to 164/88 mm Hg with HCTZ monotherapy (*P* value not reported). At 4 weeks standing blood pressure fell from a mean of 164/88 mm Hg at the end of the 2-week HCTZ monotherapy period to 145/811 mm Hg at 2 weeks with combination therapy (*P* value not reported). At 18 weeks standing blood pressure fell from a mean of 166/90 mm Hg at baseline to 132/80 mm Hg with combination therapy (*P* value not reported). Secondary: Not reported
Channick et al[25] Combination chlorthalidone 50 mg/day and reserpine 0.25 mg/day vs combination methyldopa 250 mg/day and HCTZ 15 mg/day	OL, RCT Patients with hypertension	N=56 12 weeks	Primary: Efficacy of blood pressure lowering to goal DBP ≤90 mm Hg Secondary: Adverse effects	Primary: Goal DBP of ≤ 90 mm Hg was reached in 91% of the chlorthalidone and reserpine group vs 55% in the methyldopa and HCTZ group (*P*<0.001). Secondary: The incidence of adverse effects was 31% with chlorthalidone and reserpine vs 64% with methyldopa and HCTZ (*P*<0.02).
Weber et al[26] Chlorthalidone 15 mg/day and clonidine 0.1 mg/day combination entity; if response inadequate after 2 weeks, combination was increased to	DB, PC, RCT Men > 60 years old with isolated systolic hypertension (supine SBP ≥160 mm Hg and DBP ≤100 mm	N=24 12 weeks	Primary: Blood pressure lowering efficacy Secondary: Adverse effects	Primary: SBP dropped significantly in both the supine and upright postures in the active treatment group (*P*<0.001). No significant change in the placebo group. DBP dropped significantly in both the supine and upright postures in the active group (*P*<0.05). No significant change in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
twice daily vs placebo	Hg)			Secondary: Active treatment induced small decreases in potassium and small increases in uric acid levels ($P<0.01$) and induced an increase in the aldosterone excretion rate ($P<0.05$). However, no significant changes in creatinine clearance (*P* value not reported).
Rosenman et al[27] Combination chlorthalidone and clonidine once-daily therapy (doses not reported)	OL, RCT Patients with essential hypertension	N=30 2 years	Primary endpoint: Blood pressure lowering efficacy Secondary: Adverse effects	Primary: Patients on combination therapy experienced 12.9% to 16.4% enhanced blood pressure lowering effect vs patients on diuretic monotherapy (*P* value not reported). Secondary: Side effects were mild and mainly included dry mouth and drowsiness (*P* value not reported). Orthostatic hypotension was seen in 3 patients receiving combination therapy; however, it was relatively mild and subsided upon dose adjustment (*P* value not reported).
Fernandez et al[28] Methyldopa 750 mg/day vs chlorothiazide 450 mg/day vs methyldopa 250 mg and chlorothiazide 150 mg/day combination entity vs placebo	DB, PC, RCT, XO Patients with uncomplicated hypertension	N=44 4 weeks	Primary: Blood pressure Lowering efficacy Secondary: Adverse effects	Primary: No significant differences in supine blood pressures for any treatment arm vs placebo (*P* value not reported). However, upright SBP, DBP, and mean blood pressures were significantly lower after treatment with methyldopa or combination therapy vs treatment with placebo ($P<0.05$). Secondary: Adverse effects were reported as infrequent (*P* value not reported).

Study abbreviations: DB=double-blind, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Combination Central α-Agonists

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
clonidine and chlorthalidone	tablet	Clorpres®*	$$	$
methyldopa and hydrochlorothiazide	tablet	Aldoril®*	N/A	$

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

X. Conclusions

The central α-agonists are one of the oldest drug therapies in the antihypertensive class. The mechanism of action of these agents allows for the reduction of total peripheral resistance. As a result, these agents may be useful in certain patients with underlying diseases, which may be worsened by other antihypertensive agents, such as chronic obstructive pulmonary disease or peripheral vascular disease. Methyldopa remains the drug of choice for pregnant women due to its safety profile.[4]

Central α-agonists are often used in combination with diuretics. Using both agents in combination may allow lower doses to be used for either or both drugs. [4] Concomitant use of a diuretic and methyldopa may also prevent sodium retention and increased plasma volume that may occur after prolonged methyldopa therapy.[5] Regardless, central α-agonists are not recommended as initial therapy of hypertension primarily because of their significant side effect profiles and the potential for severe rebound hypertension upon rapid withdrawal.[29] Additionally, for

those patients requiring combination therapy for hypertension management, currently there is a vast array of better tolerated and well-accepted combination products (both brand and generic) from other antihypertensive categories.

There are limited head-to-head trials comparing the combination central α-agonists. Overall, the available data demonstrates comparable safety and efficacy among the combination central α-agonists. Clonidine and chlorthalidone, and methyldopa and hydrochlorothiazide are available as generic combination products..

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand combination central α-agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Direct Vasodilators
Single Entity Agents
AHFS Class 240820
September 10, 2008

I. Overview

Direct vasodilators are not recommended as first-line therapies in the treatment of hypertension according to guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[1] Direct vasodilators are effective as add on therapy in patients with refractory or severe uncontrolled hypertension despite optimal treatment with standard pharmacological therapy. [2] They are not usually successful as monotherapy and work best in combination with other antihypertensive drugs.[3]

The single entity direct vasodilators are thought to function through a peripheral-vasodilating effect, which results in the direct relaxation of vascular smooth muscle.[3] This in turn results in decreased arterial blood pressure (diastolic more than systolic); decreased peripheral vascular resistance; and a compensatory increase in heart rate, stroke volume, and cardiac output.[3]

Diazoxide, when administered orally, does not demonstrate these same effects on blood pressure but rather produces a prompt dose-related increase in blood glucose levels, due primarily to an inhibition of insulin release from the pancreas and also to an extrapancreatic effect.[4] Oral diazoxide is the first-line therapy for hypoglycemia due to hyperinsulinism or insulin overproduction in patients who are not candidates for surgery.[5] Conditions associated with excess insulin production include insulinoma, persistent hyperinsulinemic hypoglycemia of infancy or primary islet-cell hyperplasia and noninsulinoma pancreatogenous hypoglycemia.

The single entity direct vasodilators that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Hydralazine and minoxidil are available generically. Nitroprusside sodium and the intravenous formulation of diazoxide are administered primarily on an inpatient basis in institutions. Since they are not routinely dispensed in an outpatient pharmacy, they have not been included in this review.

Table 1. Single Entity Direct Vasodilators Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
diazoxide	injection^, oral suspension	Hyperstat IV®^, Proglycem®	none
hydralazine	injection^, tablet	N/A	hydralazine
minoxidil	tablet	Loniten®†*	minoxidil
nitroprusside sodium	injection^	Nitropress®^	none

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
^Product is primarily administered in an institution.
N/A=not available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the treatment of hypertension are listed in Table 2. The single entity direct vasodilators are listed in the majority of treatment guidelines; however, there are no specific recommendations for these drugs. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Single Entity Direct Vasodilators

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[1]	• Pregnant women with hypertension should be treated with β-adrenergic blocking agents (β-blockers), methyldopa, or vasodilators. • No specific recommendation is made concerning single entity direct vasodilators.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[6]	• No specific recommendation is made concerning single entity direct vasodilators.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[7]	• No specific recommendation is made concerning single entity direct vasodilators.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[8]	• No specific recommendation is made concerning single entity direct vasodilators.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[9]	• No specific recommendation is made concerning single entity direct vasodilators.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[10]	• No specific recommendation is made concerning single entity direct vasodilators.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes-2008**[11]	• No specific recommendation is made concerning single entity direct vasodilators.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[12]	• No specific recommendation is made concerning single entity direct vasodilators.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[13]	• No specific recommendation is made concerning single entity direct vasodilators.

III. Indications

Food and Drug Administration (FDA)-approved indications for the single entity direct vasodilators 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 Single Entity Direct Vasodilators[4,14-16]

Indication	Diazoxide	Hydralazine	Minoxidil
Hypertension		✔ *	✔ †
Emergency reduction of blood pressure in severe, nonmalignant and malignant hypertension in hospitalized adults; and in acute severe hypertension in hospitalized children	✔ (intravenous)		
Hypoglycemia due to hyperinsulinism	✔ ‡(oral)		

*Alone or in combination with other agents.
†Approved only for hypertension that is symptomatic or associated with target organ damage and is not manageable with maximum therapeutic doses of a diuretic plus two other antihypertensive drugs.
‡In adults: hyperinsulinism associated with inoperable islet cell adenoma or carcinoma, or extrapancreatic malignancy. In children: hyperinsulinism associated with leucine sensitivity, islet cell hyperplasia, nesidioblastosis, extrapancreatic malignancy, islet cell adenoma, or adenomatosis.

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity direct vasodilators are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Single Entity Direct Vasodilators[4,14,15,17]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Diazoxide	Unknown	90	Partially, oxidation and sulfate conjugation	Not reported	Not reported	Renal	20-36
Hydralazine	38-50	85-87	Liver; acetylation, hydroxylation, conjugations with glucuronic acid	None to minimal activity	3-14	Renal	3-7
Minoxidil	90	Insignificant	Liver (90%) glucuronidation	Yes, Minoxidil-0-glucuronide	Not reported	Renal	4.2

V. Drug Interactions

Significant drug interactions with the single entity direct vasodilators are listed in Table 5. There were no drug interactions of major or moderate severity reported for minoxidil.

Table 5. Significant Drug-Drug Interactions With the Single Entity Direct Vasodilators[18]

Drugs	Significance Level	Interaction	Mechanism
Diazoxide	2	Hydantoins (fosphenytoin, phenytoin)	Serum phenytoin levels may be decreased, resulting in a possible decrease in the anticonvulsant actions of phenytoin.
Diazoxide	2	Sulfonylureas (acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide, tolbutamide)	The addition of diazoxide to the regimen of a non-insulin dependent diabetic stabilized on sulfonylurea therapy may result in hyperglycemia.
Diazoxide	2	Thiazide-type diuretics (Bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclothiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, quinethazone, trichlormethiazide)	Hyperglycemia may occur with symptoms similar to diabetes. The mechanism is unknown.
Hydralazine	2	β-adrenergic blocking agents (β-blockers) (metoprolol, propranolol)	Serum levels and hence, pharmacologic effects of both drugs may be enhanced. Hydralazine increases systemic availability of some β-blockers, probably by transient increase in splanchnic blood flow and decreasing first-pass hepatic metabolism

Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse reactions reported with the single entity direct vasodilators are noted in Table 6. A black box warning, reproduced in Table 7, has been mandated for minoxidil due to the risk of serious cardiac adverse events.

Table 6. Adverse Drug Events (%) Reported With the Single Entity Direct Vasodilators [4,14,15,17]

Adverse Event	Diazoxide	Hydralazine	Minoxidil
Cardiovascular System			
Angina pectoris	-	✔	✔
Chest pain	✔	-	-
Congestive heart failure	✔	-	>10
Edema	✔	✔	7
Electrocardiogram (transient changes in T-wave amplitude and direction	-	-	60
Flushing	-	✔	-
Hypotension	✔	✔	-
Palpitations	✔	✔	-
Paradoxical pressor response	-	✔	-
Pericardial tamponade	-	-	✔
Pericarditis	-	-	✔
Tachycardia	✔	✔	✔
Central Nervous System			
Anxiety	✔	✔	-
Asthenia	-	✔	-
Depression	-	✔	-
Disorientation	-	✔	-
Dizziness	✔	✔	-
Fever	✔	✔	-
Headache	✔	✔	✔
Malaise	✔	-	-
Endocrine			
Diabetic ketoacidosis	✔	-	-
Fluid and electrolyte imbalance	-	-	1-10
Gastrointestinal			
Abdominal pain	✔	-	-
Anorexia	✔	✔	-
Constipation	-	✔	-
Diarrhea	✔	✔	-
Nausea	✔	✔	✔
Paralytic ileus	-	✔	-
Vomiting	✔	✔	✔
Genitourinary			
Difficulty in urination	-	✔	-
Hematological			
Agranulocytosis	-	✔	-
Decreased hematocrit	✔	-	✔
Decreased hemoglobin	✔	✔	✔
Eosinophilia	✔	✔	-
Excessive bleeding	✔	-	-
Leukopenia	-	✔	✔
Lymphadenopathy	✔	✔	-
Splenomegaly	-	✔	-
Thrombocytopenia	✔	-	✔
Hepato-renal			
Albuminuria	✔	-	-
Decreased creatine clearance	✔	-	-
Decreased urinary output	✔	-	-
Hematuria	✔	-	-
Increased alkaline phosphatase	✔	-	✔
Increased aspartate aminotransferase	✔	-	-

Adverse Event	Diazoxide	Hydralazine	Minoxidil
Increased blood urea nitrogen	-	-	✔
Increased serum creatine	-	-	✔
Hypersensitivity Reaction			
Chills	-	✔	-
Pruritus	✔	✔	-
Rash	✔	✔	✔
Urticaria	-	✔	-
Neuromuscular and Skeletal			
Arthralgia	-	✔	-
Muscle cramps	-	✔	-
Numbness	-	✔	-
Tingling	-	✔	-
Tremor	✔	✔	-
Weakness	-	✔	-
Respiratory			
Dyspnea	-	✔	-
Nasal congestion	-	✔	-
Myalgia	-	✔	-
Ocular			
Blurred vision	✔	-	-
Conjunctivitis	-	✔	-
Lacrimation	-	✔	-
Transient cataracts	✔	-	-
Miscellaneous			
Drug-induced lupus-like syndrome	-	✔	-
Galactorrhea	✔	-	-
Gout	✔	-	-
Hirsutism	✔	-	-
Hypertrichosis	-	-	80
Positive antinuclear antibody	-	✔	-
Positive direct Coombs' test	-	✔	-
Positive lupus erythematosus cells	-	✔	-

- Event not reported or incidence <1%.
✔ Percent not specified.

Table 7. Black Box Warning for Minoxidil[15]

Warning
Minoxidil tablets contain the powerful antihypertensive agent, minoxidil, which may produce serious adverse effects. It can cause pericardial effusion, occasionally progressing to tamponade, and angina pectoris may be exacerbated. Minoxidil should be reserved for hypertensive patients who do not respond adequately to maximum therapeutic doses of a diuretic and two other antihypertensive agents. In experimental animals, minoxidil caused several kinds of myocardial lesions as well as other adverse cardiac effects. Minoxidil must be administered under close supervision, usually concomitantly with therapeutic doses of a beta-adrenergic blocking agent to prevent tachycardia and increased myocardial workload. It must also usually be given with a diuretic, frequently one acting in the ascending limb of the loop of Henle, to prevent serious fluid accumulation. Patients with malignant hypertension and those already receiving guanethidine should be hospitalized when minoxidil is first administered so that they can be monitored to avoid too rapid or large orthostatic decreases in blood pressure.

VII. Dosing and Administration

The usual dosing regimens for the single entity direct vasodilators are summarized in Table 8.

Table 8. Usual Dosing for the Single Entity Direct Vasodilators[4,14,15]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Diazoxide	Initial: 3 mg/kg daily, divided into 3 equal doses every 8 hours; maintenance: 3 to 8 mg/kg divided into 2 or 3 equal doses every 8 to 12 hours	Pediatrics: same as adult dose Infants and newborns: Initial, 10 mg/kg daily in 3 equal doses every 8 hours; maintenance: 8 to 15 mg/kg daily divided into 2 or 3 equal doses every 8 to 12 hours	Suspension: 50 mg/mL Ampule: 300 mg/20 mL*
Hydralazine	Initial: 10 mg 4 times daily; maintenance: 50 mg 4 times daily; maximum: 300 mg daily	Though safety and effectiveness in children have not been established in controlled clinical trials, there is experience with use in children. Initial: 0.75 mg/kg daily in 4 divided doses; maximum: 7.5 mg/kg daily or 200 mg daily	Tablet: 10 mg 25 mg 50 mg 100 mg Vial: 20 mg/mL*
Minoxidil	Initial: 5 mg daily, increase gradually every 3 days; maintenance: 10 to 40 mg daily in single or divided doses; maximum: 100 mg daily	Initial: 0.2 mg/kg daily; maintenance: 0.25 to 1 mg/kg daily; maximum: 50 mg daily	Tablet: 2.5 mg 10 mg

*Product is primarily administered in an institution.

VIII. Effectiveness

An evidence-based medicine literature search did not reveal data pertinent to the use of diazoxide for the treatment of hypoglycemia due to hyperinsulinism. There are limited comparative trials regarding the single entity direct vasodilators. The available clinical trials evaluating the safety and efficacy of the single entity direct vasodilators are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Single Entity Direct Vasodilators

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Johnson et al[19] Minoxidil 5 to 40 mg/day as add-on therapy vs hydralazine 25 to 200 mg/day as add-on therapy	DB, RCT Patients with normal renal function receiving HCTZ or propranolol (doses unknown) with DBP >95 mm Hg	N=36 28 weeks	Primary: Percentage of patients with DBP <90 mm Hg at weeks 4 and 28 Secondary: Not reported	Primary: There were greater response rates (DBP <90 mm Hg) with minoxidil (69%) vs hydralazine (35%) at week 4 (no *P* value reported). At week 28, there were greater response rates (DBP <90 mm Hg) with minoxidil (55%) vs hydralazine (40%; no *P* value reported). Secondary: Not reported
Bevan et al[20] Captopril (unknown dose) vs hydralazine (unknown dose) vs nifedipine (unknown dose) vs placebo	DB, PC, RCT Patients with inadequately controlled hypertension, despite treatment with atenolol 100 mg/day and bendrofluazide* 5 mg/day	N=160 12 weeks	Primary: Comparative antihypertensive, biochemical, and adverse effects Secondary: Not reported	Primary: Mean supine blood pressure changes: captopril 13.4/10.3 mm Hg, hydralazine 15.0/10.0 mm Hg, and nifedipine 16.8/8.1 mm Hg (differences not significant). Erect blood pressure changes were similar; target blood pressure (<140/95 mm Hg) was achieved in 33% with captopril, 29% with hydralazine, 17% with nifedipine, and 10% with placebo. Compared with other agents, captopril increased serum potassium (value not reported; *P*=0.01). Mean changes in serum cholesterol: captopril -0.2 mmol/L, hydralazine -0.8 mmol/L, nifedipine -0.2 mmol/L, and placebo +0.2 mmol/L (*P*<0.001). Side effects did not differ significantly between the groups. Withdrawal rates: captopril 15%, hydralazine 24%, nifedipine 22%, and placebo 3% (*P*=0.04). Secondary: Not reported
Julien et al[21]	DB, PG, RCT	N=34	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Captopril 150 to 300 mg/day vs minoxidil 7.5 to 30 mg/day	Male patients with left ventricular hypertrophy and essential hypertension with DBP >95 mm Hg who were taking metoprolol 200 mg/day and furosemide 80 mg/day	6 months	Blood pressure changes and left ventricular hypertrophy changes as seen on electrocardiogram Secondary: Not reported	Blood pressure decreased significantly in both groups; captopril (163/102 to 135/89 mm Hg) and minoxidil (160/99 to 137/87 mm Hg; $P<0.001$). Electrocardiogram criteria for left ventricular hypertrophy improved with captopril only with a decrease in intraventricular septum, posterior wall, and left ventricular mass (17.4 to 15.9 mm; $P<0.05$, 14.5 to 13.4 mm; $P<0.05$ and 236 to 198 g/m^2; $P<0.001$, respectively). No changes on electrocardiogram criteria with minoxidil. Secondary: Not reported
McAreavey et al[22] Hydralazine 12.5 mg QD up to 100 mg BID vs labetalol 200 mg QD up to 1,600 mg BID vs methyldopa 125 mg QD up to 1,000 mg BID vs prazosin 0.5 mg QD up to 10 mg BID vs placebo Minoxidil as add-on therapy was given to men only.	DB, PG, RCT Patients with inadequately controlled hypertension while taking atenolol 100 mg/day and bendrofluazide* 5 mg/day	N=238 6 months	Primary: Comparative safety and efficacy, target blood pressure <140/95 mm Hg Secondary: Not reported	Primary: Target blood pressure goal was reached in 25% of hydralazine group, 23% with minoxidil, 19% with prazosin, 17% with methyldopa, and 0% with placebo. Labetalol had the highest withdrawal rate 78% ($P<0.05$) vs other groups. Minoxidil had the second highest withdrawal rate 57% ($P<0.05$) due to fluid retention. There were no significant differences in withdrawal rates among the other groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Doses were titrated upward at 2-week intervals until target blood pressure or maximum dose was reached.				

*Synonym for bendroflumethiazide.
Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: DB=double-blind, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity Direct Vasodilators

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
diazoxide	injection, oral suspension	Hyperstat IV®, Proglycem®	$$$$$	N/A
hydralazine	injection, tablet	N/A	N/A	$
minoxidil	tablet	Loniten®†*	N/A	$
nitroprusside sodium^	injection	Nitropress®	$$$	N/A

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

The single entity direct vasodilators are not considered first-line therapy for hypertension according to current clinical guidelines.[1,6-13] Clinical studies demonstrate that the single entity direct vasodilators, hydralazine and minoxidil, are efficacious in the treatment of hypertension when added to existing regimens in patients whose blood pressure is inadequately controlled.[19-22] The single entity direct vasodilators are associated with a number of potentially severe adverse effects, which limit their use. For these reasons, the single entity agents are rarely used as monotherapy.

There are limited head-to-head trials comparing the single entity direct vasodilators. The existing clinical trials are relatively small and of short duration. Overall, the available data does not consistently demonstrate that one single entity direct vasodilator is safer or more effective than another. Hydralazine and minoxidil are only available generically.

Hypoglycemia is an uncommon clinical condition in patients without diabetes mellitus. In the treatment of hypoglycemia secondary to hyperinsulinism, oral diazoxide is considered a first-line agent.[3] In light of oral diazoxide's limited labeled indication; it is advisable that this agent be managed through the existing medical justification portion of the prior-authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity direct vasodilator is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Direct Vasodilators
Combination Products
AHFS Class 240820
September 10, 2008

I. Overview

Hydralazine, a single entity direct vasodilator, is available in combination with hydrochlorothiazide or with isosorbide dinitrate. The fixed-dose combination hydralazine plus hydrochlorothiazide is indicated for the management of hypertension and hydralazine plus isosorbide dinitrate is indicated as an adjunct to standard therapy for heart failure in self-identified African American patients. Direct vasodilators have limited effectiveness as single agents and are not usually used as monotherapy. The addition of a direct vasodilator to other agents for hypertension or heart failure should be considered mainly in patients who have not responded adequately to recommended first-line drug regimens.[1-4]

All direct vasodilators function through a direct vasodilatory effect on vascular smooth muscle.[5,6] This vasodilation results in decreased arterial blood pressure (diastolic more than systolic), decreased peripheral vascular resistance, and a compensatory increase in heart rate, stroke volume, and cardiac output.[6,7] Another compensatory response is decreased renal sodium excretion and increased plasma volume; consequently, a diuretic such as hydrochlorothiazide is often used to offset this effect.[6,7]

The organic nitrates induce relaxation of vascular smooth muscles, resulting in dilation of peripheral arteries and veins.[8-10] Venous dilation reduces left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). The dilation of the arteries causes a reduction in systemic vascular resistance, systolic arterial pressure and mean arterial pressure (afterload).[11,12] The vasodilatory effects of nitrates are least pronounced in the arterioles, and this selective vasodilation can have useful effects, as when nitrates are used to treat angina.[8,9] In the treatment of heart failure, hydralazine and nitrates are sometimes used in combination because hydralazine selectively dilates arterioles.[2-4,6,8,10] Frequent repeated or continuous exposure to organic nitrates leads to a decrease in their pharmacological effects. Tolerance to nitrates is a result of dose and frequency of administration of the preparation. The development of tolerance limits the efficacy of all chronic nitrate therapies regardless of route. Nitrate-free interval dosing can limit the degree of tolerance produced from chronic nitrate therapy.[9]

The combination product containing hydralazine and isosorbide dinitrate (BiDil®) is currently not available generically. Additionally, in January 2008, NitroMed Inc, the manufacturer of BiDil®, announced that it was discontinuing sales and promotional activities for BiDil® although it will continue to make it available for patients.[13] NitroMed also reported its intentions to proceed with development of a longer-acting, once-daily version of BiDil®.[13]

The combination direct vasodilators that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Combination Direct Vasodilators Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
hydralazine and hydrochlorothiazide	capsule	Apresazide®*†	hydralazine and hydrochlorothiazide
hydralazine and isosorbide dinitrate	tablet	BiDil®	none

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the combination direct vasodilators are summarized in Table 2. The combination direct vasodilators are listed in the majority of treatment guidelines; however, there are not always specific recommendations for these agents. For a comprehensive overview of the pharmacologic management of congestive heart failure and hypertension please refer to the Appendix.

Table 2. Treatment Guidelines Using the Combination Direct Vasodilators

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[2]	Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. • The addition of a nitrate and hydralazine is reasonable in patients with reduced left ventricular ejection fraction already on an angiotensin-converting enzyme (ACE) inhibitor and β-blocker and who have persistent symptoms. • The combination of a nitrate and hydralazine is reasonable in patients who are intolerant to ACE inhibitor and angiotensin receptor blocker (ARB) therapy or in whom therapy with one of these agents is contraindicated. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • Diuretics are recommended to control pulmonary congestion and peripheral edema. Special Populations • Hydralazine and isosorbide dinitrate may be beneficial when added to the standard treatment including β-adrenergic blocking agents (β-blockers) and ACE inhibitors in African American patients with New York Heart Association (NYHA) functional class III or IV. Patients With Concomitant Disorders • All recommendations should apply to patients with concomitant disorders unless exceptions exist. • Nitrates and β-blockers are recommended in patients with heart failure and angina.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[3]	Patients With Left Ventricular Systolic Dysfunction • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • A combination of hydralazine and an oral nitrate is recommended in African American patients who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients who are symptomatic despite optimization of standard therapy. • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics are typically preferred. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • Diuretics are recommended in patients with evidence of fluid overload. Patients With Acute Decompensated Heart Failure • Intravenous vasodilators, diuretics, and inotropes have all been used to treat patients with acute decompensated heart failure.

Clinical Guideline	Recommendation
	Patients With Heart Failure and Coronary Artery Disease • Nitrates may be considered in patients who need additional management for symptomatic angina. Managing Patients With Heart Failure and Hypertension • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing calcium channel blocking agent (amlodipine) may be considered. Managing Heart Failure in the Elderly, Women, and African Americans • Hydralazine and isosorbide dinitrate are recommended in all African American patients (in addition to standard therapy with ACE inhibitors and β-blockers) with left ventricular systolic dysfunction who are in NYHA classes II-IV.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)[4]**	• Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated. • A combination of hydralazine and isosorbide dinitrate may be tried in patients who are intolerant to ACE inhibitors and ARBs. • Nitrates may be considered in patients with comorbid angina.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)[1]**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia. • No specific recommendation is made concerning combination direct vasodilators.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)[14]**	• If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • No specific recommendation is made concerning combination direct vasodilators.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)[15]**	• Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the

Clinical Guideline	Recommendation
	following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated. • No specific recommendation is made concerning combination direct vasodilators.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[16]	• Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment. • No specific recommendation is made concerning combination direct vasodilators.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[17]	• No specific recommendation is made concerning combination direct vasodilators.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[18]	• No specific recommendation is made concerning combination direct vasodilators.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[19]	• Multiple drug therapy is generally required to achieve blood pressure goals. • No specific recommendation is made concerning combination direct vasodilators.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[20]	• No specific recommendation is made concerning combination direct vasodilators.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[21]	• If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • No specific recommendation is made concerning combination direct vasodilators.

III. Indications

Food and Drug Administration (FDA)-approved indications for the combination direct vasodilators 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 Combination Direct Vasodilators[11,22]

Indication	Hydralazine and Hydrochlorothiazide	Hydralazine and Isosorbide Dinitrate
Hypertension	✔	
Heart failure, as an adjunct to standard therapy in self-identified black patients		✔

IV. Pharmacokinetics

The pharmacokinetic parameters for the combination direct vasodilators are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Combination Direct Vasodilators[6,11,12,22]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Hydro-chlorothiazide	50-75	40-68	Not appreciably metabolized	Not reported	>95	Urine	6-15
Hydralazine	38-50	85-87	Liver: acetylation, hydroxylation, conjugations with glucuronic acid	None to minimal activity	3-14	Renal	3-7
Isosorbide Dinitrate	10-90	28	Extensive First-pass metabolism in liver	Yes, 2-mononitrate and 5-mononitrate	80-90	Renal	1-4

V. Drug Interactions

Significant drug interactions with the combination direct vasodilators are listed in Table 5.

Table 5. Significant Drug-Drug Interactions With the Combination Direct Vasodilators[23]

Drugs	Significance Level	Interaction	Mechanism
Hydrochlorothiazide	1	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Hydrochlorothiazide	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Nitrates and nitrites	1	Sildenafil, tadalafil, vardenafil	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.
Hydralazine	2	β-adrenergic blocking agents (β-blockers) (metoprolol, propranolol)	Serum levels and hence, pharmacologic effects of both drugs may be enhanced. Hydralazine increases systemic availability of some β-blockers, probably by transient increase in splanchnic blood flow and decreasing first-pass hepatic metabolism
Hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and

Drugs	Significance Level	Interaction	Mechanism
			urine glucose levels should be frequently monitored, and dosage reductions may be required.
Hydrochlorothiazide	2	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Hydrochlorothiazide	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate carefully in small or intermittent doses.
Hydrochlorothiazide	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.
Nitrates and nitrites	2	Dihydroergotamine	The metabolism of dihydroergotamine is decreased thus increasing its bioavailability. The dose of the dihydroergotamine may need to be decreased.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse reactions reported with the combination direct vasodilators are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported With the Combination Direct Vasodilators[6,11,12,22,24]

Adverse Event	Isosorbide Dinitrate and Hydralazine	Hydralazine	Hydrochlorothiazide
Cardiovascular System			
Angina pectoris	-	✔	-
Chest pain	16	-	-
Edema	-	✔	-
Flushing	-	✔	-
Hypotension	8	✔	1-10
Orthostatic hypotension	-	-	1-10
Palpitations	4	✔	-
Paradoxical pressor response	-	✔	-
Pulmonary Edema	-	-	✔
Tachycardia	2-4	✔	-
Central Nervous System			
Anxiety	-	✔	-
Asthenia	14	✔	-
Depression	-	✔	-
Disorientation	-	✔	-
Dizziness	32	✔	✔
Fever	-	✔	-
Headache	50	✔	✔

Adverse Event	Isosorbide Dinitrate and Hydralazine	Hydralazine	Hydrochlorothiazide
Malaise	1-2	✔	-
Peripheral neuritis	-	✔	-
Somnolence	1-2	-	-
Vertigo	-	-	✔
Dermatologic			
Alopecia	1-2	-	-
Angioedema	1-2	-	-
Paresthesia	4	-	-
Photosensitivity	-	-	1-10
Sweating	1-2	-	-
Endocrine/Metabolic			
Diaphoresis	-	✔	-
Glycosuria	-	-	✔
Hypercholesterolemia	1-2	-	-
Hyperglycemia	4	-	✔
Hyperlipidemia	3	-	-
Hypokalemia	-	-	1-10
Impotence	-	✔	-
Gastrointestinal			
Anorexia	-	✔	1-10
Bowel incontinence	✔	-	-
Cholecystitis	1-2	-	-
Constipation	-	✔	✔
Diarrhea	-	✔	✔
Epigastric distress	-	-	1-10
Nausea	10	✔	✔
Paralytic ileus	-	✔	-
Vomiting	4	✔	✔
Genitourinary			
Difficulty in urination	-	✔	-
Hematological			
Agranulocytosis	-	✔	✔
Decreased hematocrit	-	-	-
Decreased hemoglobin	-	✔	-
Eosinophilia	-	✔	-
Leukopenia	-	✔	✔
Splenomegaly	-	✔	-
Thrombocytopenia	-	-	✔
Hypersensitivity Reaction			
Allergic reaction	1-2	-	-
Pruritus	-	✔	-
Rash	-	✔	✔
Urticaria	-	✔	✔
Neuromuscular and Skeletal			
Arthralgia	1-2	✔	-
Muscle cramps	-	✔	-
Muscle spasm	-	-	✔
Myalgia	1-2	✔	-
Tendon disorder	1-2	-	-
Tremor	-	✔	-
Weakness	-	✔	✔
Respiratory			

Adverse Event	Isosorbide Dinitrate and Hydralazine	Hydralazine	Hydrochlorothiazide
Bronchitis	8	-	-
Dyspnea	-	✔	-
Nasal congestion	-	✔	-
Rhinitis	4	-	-
Sinusitis	8	-	-
Ocular			
Amblyopia	3	-	-
Blurred vision	✔	-	✔
Conjunctivitis	-	✔	-
Lacrimation	-	✔	-
Miscellaneous			
Drug-induced lupus-like syndrome	-	✔	-
Lymphadenopathy	-	✔	-
Positive antinuclear antibody	-	✔	-
Positive direct Coombs' test	-	✔	-
Positive lupus erythematosus cells	-	✔	-

- Event not reported or incidence <1%.
✔ Percent not specified.

VII. Dosing and Administration

Combination fixed-dose hydralazine and isosorbide dinitrate is not interchangeable with the associated individual components. However, the individual components are available generically in several dosage strengths, which allows for appropriate titration. The usual dosing regimens for the combination direct vasodilators are summarized in Table 7.

Table 7. Usual Dosing for the Combination Direct Vasodilators[11,22,23]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Hydralazine and hydrochlorothiazide	Dosage should be determined by individual titration. Maintenance: 1 capsule 2 times daily	The safety and effectiveness in children have not been established.	Capsule: 25 mg-25 mg 50 mg-50 mg 100 mg-50 mg
Hydralazine and isosorbide dinitrate	Initial: 1 tablet (37.5 mg-20 mg) 3 times daily; maximum: 2 tablets 3 times daily	The safety and effectiveness in children have not been established.	Tablet: 37.5 mg-20 mg

VIII. Effectiveness

An evidence-based medicine literature search did not reveal data pertinent to clinical trials data involving the use of the combination product hydralazine and hydrochlorothiazide. Therefore, the clinical data included below focuses primarily on the combination product hydralazine and isosorbide dinitrate. Clinical studies evaluating the safety and efficacy of the combination direct vasodilators are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Combination Direct Vasodilators

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Unverferth et al[25] Hydralazine 225 mg/day vs ISDN 160 mg/day vs hydralazine and ISDN (individual agents, concurrent therapy) vs placebo	DB, PC, RCT Patients with idiopathic dilated cardiomyopathy were evaluated to determine the hemodynamic and morphologic effects of vasodilator therapy	N=49 3 months	Primary: Echocardiographic percent change of left ventricular diameter (% Δ), the systolic time intervals ratio of PEP/LVET, the pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, and SVR Secondary: Not reported	Primary: For the % Δ of left ventricular diameter and PEP/LVET, a significant improvement with hydralazine and combination therapy (P<0.05) was seen compared to ISDN alone or placebo. Significant decrease with ISDN and combination therapy vs placebo or hydralazine alone (P<0.05) was seen for pulmonary capillary wedge pressure, mean pulmonary artery pressure, and the pulmonary vascular resistance. Hydralazine resulted in a decrease in SVR and increase in cardiac index from 2.5±0.4 to 3.1±0.4 L/min/m^2 vs placebo or ISDN alone (P<0.05). Combination therapy resulted in a decrease in SVR and cardiac index increased from 2.3±0.4 to 3.1±0.4 L/min/m^2 (P<0.01). There was no improvement in SVR or cardiac index with ISDN alone or with placebo. Myocardial cell diameter decreased from 25.4±3.1 microns at baseline to 23.1±3.8 microns with hydralazine (P<0.05). Combination therapy decreased its cell diameter from 23.9±3.7 to 22.2±2.2 microns (P<0.05). There was no change in the myocardial cell diameter seen in patients treated with ISDN alone or with placebo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
African-American Heart Failure Trial (A-HeFT)[26] Hydralazine 112.5 mg/day with ISDN 60 mg/day in 3 divided doses titrated up to hydralazine 225 mg/day with ISDN 120 mg/day in 3 divided doses (fixed-dose combination) vs placebo	DB, MC, PC, RCT African American patients with moderate-to-severe symptomatic heart failure, classified NYHA class III-IV heart failure with dilated ventricles and low ejection fractions	N=1,050 6-18 months	Primary: Composite score (all-cause mortality, first hospitalization for heart failure, and quality of life at 6 months as measured by the Minnesota Living with Heart Failure questionnaire) Secondary: Not reported	Primary: Mortality in the fixed-dose hydralazine-ISDN group was 6.2% compared with 10.2% in the placebo group (*P*=0.02). Survival was increased by 43% in the active treatment arm (HR, 0.57; *P*=0.02). The composite score and all individual components of the composite score were significantly and positively impacted by treatment with hydralazine-ISDN (primary composite score *P*=0.01, death from any cause *P*=0.02, first hospitalization for heart failure *P*=0.001, change in quality of life score at 6 months *P*=0.02). The study was prematurely terminated in as a result of the significantly improved survival in the hydralazine-ISDN group. Secondary: Not reported
Taylor et al[27] A-HeFT Hydralazine 37.5 mg plus ISDN 20 mg TID increased to hydralazine 75 mg plus ISDN 40 mg TID (fixed-dose combination) 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 at least 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, and quality of life changes Secondary: Individual components of the primary composite score	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 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 hydralazine plus ISDN when compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(–5.6±20.6 vs –2.7±21.2; *P*=0.02). Secondary: Results of individual components were not reported.
Taylor et al[28] A-HeFT Hydralazine 37.5 mg plus ISDN 20 mg TID increased to hydralazine 75 mg plus ISDN 40 mg TID (fixed-dose combination) 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 at least 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: Same as study by Taylor et al[27] Secondary: Individual components of the primary composite score	Primary: Same as study by Taylor et al[27] In the treatment group event-free survival (death or first hospitalization for heart failure) was significantly improved compared with placebo (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, sex, baseline blood pressure, 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 [29] A-HeFT Hydralazine 37.5 mg plus ISDN 20 mg TID increased to hydralazine 75 mg plus ISDN 40 mg TID (fixed-dose combination) 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 at least 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: 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 placebo. There were no significant differences in adverse events between treatment 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.
Cohn et al[30]	AC, DB, PC, RCT	N=642	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
V-HeFT I Hydralazine 300 mg daily plus ISDN 160 mg daily (individual agents, concurrent therapy) vs prazosin 20 mg daily vs placebo	Men with impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic	3 years	Mortality Secondary: Effect on left ventricular function	There was a 34% risk reduction in mortality by 2 years in the hydralazine plus ISDN group compared to placebo (*P*<0.028). Cumulative mortality rates of 25.6% and 36.2% were observed in the hydralazine plus ISDN group at 2 and 3 years respectively, compared to 34.3% and 46.9% in the placebo group (*P* value not reported). The results found in the prazosin group were similar to placebo. Secondary: A significant increase in the left ventricular ejection fraction was reported at 8 weeks and 1 year in the hydralazine plus ISDN treatment group, but not in either the prazosin or placebo groups.
Cohn et al[31] V-HeFT II Enalapril 20 mg/day vs hydralazine 300 mg/day plus ISDN 160 mg/day (individual agents, concurrent therapy)	DB, RCT Men receiving digoxin and diuretic therapy for heart failure	N=804 2 years	Primary: Mortality, body oxygen consumption at peak exercise, left ventricular ejection fraction Secondary: Not reported	Primary: Mortality after two years was significantly lower in the enalapril arm (18%) than in the hydralazine-ISDN arm (25%) (*P*=0.016). Body oxygen consumption at peak exercise was increased only by hydralazine-ISDN treatment (*P*<0.05). Left ventricular ejection fraction, which increased with both regimens during the 2 years after randomization, increased more (*P*<0.05) during the first 13 weeks in the hydralazine-ISDN group. Secondary: Not reported

Study abbreviations: AC=active-controlled, DB=double-blind, HR=hazard ratio, MC=multicenter, PC=placebo-controlled, RCT=randomized control trial
Miscellaneous abbreviations: ISDN=isosorbide dinitrate, LVET=left ventricular ejection time, NYHA=New York Heart Association, PEP=pre-ejection period, SVR=systemic vascular resistance

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Combination Direct Vasodilators

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
hydralazine and hydrochlorothiazide	Capsule	Apresazide®*†	N/A	$
hydralazine and isosorbide dinitrate	Tablet	BiDil®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

There is very limited data regarding the combination product hydralazine and hydrochlorothiazide. The available literature shows that this product is not considered a first-line therapy and is reserved for use in patients who have shown an inadequate response to monotherapy and who have been stabilized on its individual components. Hydralazine is typically used as an add-on therapy to an existing multidrug antihypertensive regimen, when blood pressure is still inadequately controlled. The use of hydralazine is limited due to the drug's potential for serious adverse effects, such as tachycardia, angina pectoris, and paradoxical hypertension.[12]

Concurrent administration of hydralazine and isosorbide dinitrate has proven to be beneficial in the treatment of heart failure.[25-30] Clinical benefit was shown in studies in which hydralazine and isosorbide dinitrate were administered concomitantly as individual components[25,30] and as a fixed-dose combination product.[26-29] The V-HeFT I study reported a 34% risk reduction in mortality by 2 years in men with impaired cardiac function and

reduced exercise tolerance who received concurrent treatment with hydralazine and isosorbide dinitrate.[30] The A-HeFT trial reported lower mortality rates with the fixed-dose combination product compared to placebo in African American patients with moderate-to-severe symptomatic heart failure.[26-29] Both hydralazine (10 mg, 25 mg, 50 mg, and 100 mg) and isosorbide dinitrate are available generically; however, generic hydralazine is not available in a strength equivalent to the fixed-dose combination product, which contains 37.5 mg of hydralazine.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand combination direct vasodilator is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Peripheral Adrenergic Inhibitors
AHFS Class 240832
September 10, 2008

I. Overview

Reserpine, a crystalline alkaloid of *Rauwolfia serpentina*, is one of the oldest antihypertensive agents available. Reserpine acts in the central and peripheral sympathetic nervous systems. Reserpine depletes norepinephrine and serotonin stores both centrally and in the peripheral adrenergic nerve endings; and also acts by blocking the transport of norepinephrine into its storage granules. Reserpine also depletes catecholamines from the brain and myocardium and increases vagal tone, which may lead to decreased cardiac output, depression and sedation.[1,2] Reserpine is Food and Drug Administration (FDA) approved for the treatment of mild to moderate hypertension; although it is rarely used as monotherapy, as it is reserved as adjunctive therapy along with other antihypertensives.[2-4] Additionally, reserpine is FDA approved for the relief of symptoms in agitated psychotic states, especially in patients unable to tolerate phenothiazine derivatives or in patients also requiring antihypertensives.[3,4] Although approved for this psychiatric indication, currently available literature does not discuss the use of reserpine for psychiatric conditions, and it is not recommended in the relevant psychiatric treatment guidelines.

Table 1 lists the peripheral adrenergic inhibitors that are included in this review. This review encompasses all dosage forms and strengths.

Table 1. Peripheral Adrenergic Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
reserpine*	tablet	N/A	reserpine

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the treatment of hypertension are listed in Table 2. Reserpine is listed in the majority of treatment guidelines however; there are no specific recommendations for this drug. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Peripheral Adrenergic Inhibitors

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[5]	• Reserpine is listed as a single agent and in combination with chlorthalidone and hydrochlorothiazide for the treatment of hypertension; however, there are no specific recommendations for this drug.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[6]	• No specific recommendation is made concerning reserpine.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[7]	• No specific recommendation is made concerning reserpine.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[8]	• No specific recommendation is made concerning reserpine.

Clinical Guideline	Recommendation(s)
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[9]	• No specific recommendation is made concerning reserpine.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[10]	• No specific recommendation is made concerning reserpine.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[11]	• No specific recommendation is made concerning reserpine.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[12]	• No specific recommendation is made concerning reserpine.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[13]	• No specific recommendation is made concerning reserpine.

III. Indications

Food and Drug Administration (FDA)-approved indications for the peripheral adrenergic inhibitors are listed 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 Peripheral Adrenergic Inhibitors[4]

FDA-Approved Indications	Reserpine
The treatment of mild essential hypertension*	✔
The treatment of symptoms in agitated psychotic states (e.g., schizophrenia), primarily in those individuals unable to tolerate phenothiazine derivatives or in those who also require antihypertensive medication.	✔

*Also useful as adjunctive therapy with other antihypertensive agents in the more severe forms of hypertension.[4]

IV. Pharmacokinetics

The pharmacokinetic parameters for the peripheral adrenergic inhibitors are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Peripheral Adrenergic Inhibitors[4]

Drug	Systemic Bioavailability (%)	Protein Binding (%)	Active Metabolites	Elimination	Half-Life (hours)
Reserpine	50	95	Not reported	Renal (1% unchanged in the urine)	200

V. Drug Interactions

Significant drug interactions with the peripheral adrenergic inhibitors are listed in Table 5.

Table 5. Significant Drug-Drug Interactions for the Peripheral Adrenergic Inhibitors[14]

Drug(s)	Significance Level	Interaction	Mechanism
Reserpine (rauwolfia alkaloids)	2	Sympathomimetics (dobutamine, dopamine, ephedrine, epinephrine,	The rauwolfia alkaloids deplete the stores of catecholamines, which increases the receptor sensitivity to the direct-acting sympathomimetics while antagonizing the

Drug(s)	Significance Level	Interaction	Mechanism
		mephentermine, metaraminol, methoxamine, norepinephrine, phenylephrine)	effects of the indirect-acting agents, which release norepinephrine from the neurons. This may result in hypertension.

Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse reactions reported with the peripheral adrenergic inhibitors are noted in Table 6.

Table 6. Adverse Events (%) Reported with the Peripheral Adrenergic Inhibitors[4]

Adverse Events	Reserpine
Cardiovascular	
Angina like symptoms	✔
Arrhythmia	✔
Bradycardia	✔
Edema	✔
Syncope	✔
Central Nervous System	
Depression	✔
Dizziness	✔
Drowsiness	✔
Dull sensorium	✔
Headache	✔
Nervousness	✔
Nightmares	✔
Paradoxical anxiety	✔
Parkinsonism	Rare – Dose Dependent
Dermatological	
Pruritus	✔
Purpura	✔
Rash	✔
Gastrointestinal	
Anorexia	✔
Diarrhea	✔
Dryness of mouth	✔
Hypersecretion	✔
Nausea	✔
Vomiting	✔
Genitourinary	
Breast engorgement	✔
Decreased libido	✔
Dysuria	✔
Gynecomastia	✔
Impotence	✔
Pseudo lactation	✔
Respiratory	
Dyspnea	✔
Epistaxis	✔
Nasal congestion	✔
Other	

Adverse Events	Reserpine
Conjunctival infection	✔
Deafness	✔
Glaucoma	✔
Muscular aches	✔
Optic atrophy	✔
Uveitis	✔
Weight gain	✔

✔ Percent not specified.

VII. Dosing and Administration

The usual dosing regimens for the peripheral adrenergic inhibitors are summarized in Table 7.

Table 7. Usual Dosing for the Peripheral Adrenergic Inhibitors[4]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Reserpine	Hypertension: Initial 0.5 mg/day for 1 to 2 weeks, maintenance 0.1 to 0.25 mg/day Psychotic states: Initial 0.5 mg/day, but may initiate with 0.1 to 1.0 mg/day; dosage should then be adjusted based on patient response	Safety and efficacy has not been established in children.*	Tablet: 0.1 mg 0.25 mg

* Although reserpine is not recommended to be used in children; if it has to be used in treating a child, the usual recommended starting dose is 20 µg/kg/day with a maximum recommended dose of 0.25 mg/day.[4]

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the peripheral adrenergic inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Peripheral Adrenergic Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypertension				
Finnerty[15] Chlorthalidone 50 mg plus reserpine 0.25 mg vs HCTZ 50 mg plus reserpine 0.125 mg	CT, DB Patients with essential hypertension unresponsive to diet control and diuretic therapy	N=57 6 weeks	Primary: The change in mean DBP from baseline Secondary: Incidence of frequent or severe side effects	Primary: The chlorthalidone plus reserpine group had a mean decrease in DBP of 17.0 mm Hg at study endpoint compared with a mean decrease of 18.6 mm Hg in the HCTZ plus reserpine group (*P* values not reported). At study completion both treatment groups achieved diastolic control of at least 5 mm Hg below the targeted diastolic goal of 90 mm Hg (*P* values not reported). Secondary: There were no reports of frequent or severe side effects in either treatment group.
Finnerty et al[16] Hydroflumethiazide 50 mg or 100 mg QD plus reserpine 0.125 mg to 0.25 mg QD vs hydroflumethiazide 50 mg or 100 mg QD plus methyldopa 500 mg to 2,000 mg QD vs	CT, SB Patients with hypertension unresponsive to hydroflumethiazide alone	N=59 9 weeks	Primary: Percentage of patients achieving a DBP below 90 mm Hg Secondary: Not reported	Primary: At study endpoint, the DBP below 90 mm Hg was achieved in all 20 patients (100%) treated with hydroflumethiazide plus reserpine, 13 of the 19 patients (68.4%) treated with hydroflumethiazide plus methyldopa, and in 16 of the 20 patients (80%) treated with hydroflumethiazide plus propranolol (mean reductions and *P* values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hydroflumethiazide 50 mg or 100 mg QD plus propranolol 80 mg to 320 mg QD				
Kostis et al[17] SHEP Chlorthalidone 12.5 mg QD vs placebo If goal SBP was not achieved, the dosage of chlorthalidone was increased to 25 mg QD or matching placebo. If goal SBP still not reached, atenolol 25 mg QD or matching placebo was added. Reserpine 0.05 to 0.1 mg QD or matching placebo was used if atenolol was contraindicated (eg, asthma, congestive heart failure) or if intolerable side effects with atenolol occurred.	DB, MC, PC, RCT Persons aged ≥60 years with isolated systolic hypertension defined as a SBP 160 to 219 mm Hg and a DBP <90 mm Hg	N=4,736 4.5 years (mean)	Primary: Total mortality, fatal and nonfatal stroke combined, coronary heart disease (fatal and nonfatal myocardial infarction, sudden death, rapid death), cardiovascular disease (also including coronary heart disease and stroke) Secondary: Not reported	Primary: There were 2,365 patients randomized to active treatment and 2,371 patients randomized to placebo, with a mean follow-up of 4.5 years. Of the 2,365 patients on active treatment, 193 (8%) received reserpine for an average of 1.7 years (at risk for 2.7 person-years after first exposure); of the 193 patients, 117 (61%) received reserpine for >1 year. Conversely, 757 (32%) were on atenolol with an average exposure of 2 years (at risk for 2,311 person years after first exposure). Incident stroke was observed in 103 patients in the active group and 159 patients in the placebo (RR, 0.64; 95% CI, 0.50 to 0.82). Nonfatal myocardial infarction or coronary heart disease deaths in the active group occurred in 104 patients and 141 in the placebo group (RR, 0.73; 95% CI, 0.57 to 0.94), while 289 cardiovascular disease events occurred in the active group compared with 414 in the placebo group (RR, 0.68; 95% CI, 0.58 to 0.79). After adjustments for multiple baseline covariates, the relative risks in the reserpine group were 0.65 (95% CI, 0.26 to 1.59) for death, 0.27 (95% CI, 0.04 to 2.26) for stroke, 0.93 (95% CI, 0.29 to 2.96) for coronary heart disease events, and 0.55 (95% CI, 0.20, 1.49) for cardiovascular disease events. The relative risks in the atenolol group after adjustments for multiple baseline covariates were 0.84 (95% CI, 0.54 to 1.30) for death, 1.34 (95% CI, 0.80 to 2.28) for stroke, 1.04 (95% CI, 0.58 to 1.87) for coronary heart disease events and 1.07 (95 % CI, 0.71, 1.61) for cardiovascular disease events. Secondary outcomes: Not reported
Krönig et al[18]	AC, MC, PG, RCT	N=273	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Reserpine 0.1 to 0.2 mg QD plus clopamid* 5 to 10 mg QD vs reserpine 0.1 to 0.2 mg QD vs clopamide 5 to 10 mg QD vs nitrendipine* 20 to 40 mg QD	German patients ≥18 years with mild to moderate hypertension and a DBP of 100 to 114 mm Hg at rest	12 weeks	The change in sitting DBP and SBP from baseline to weeks 6 and 12, and the number of patients achieving the goal DBP and SBP Secondary: Changes in heart rate, incidence of adverse events, and laboratory safety parameter measurements	The reduction in DBP was similar in the reserpine, clopamide, and nitrendipine groups at week six (–11.7, –11.9, and –12.3 mm Hg), but was greater in the combination group (–17.1 mm Hg). The difference was statistically significant when the combination group was compared with each of the monotherapy groups (*P*<0.001) and the nitrendipine group (*P*=0.002). At week 12, the change in DBP compared to baseline was –12.2, –13.4, and –15.3 mm Hg in the reserpine, clopamide, and nitrendipine groups, compared to –18.1 mm Hg in the combination group. The number of patients in the combination group achieving normal DBP readings, defined as a trough <90 mm Hg) by week 6 was 55.2% compared with 39.7%, 36.2%, and 33.3% in the reserpine, clopamide, and nitrendipine groups, (*P*=0.11). Patients not achieving goal DBP at week 6 subsequently had their medication doses increased, which resulted in achievement of DBP goal in 65.7% of patients in the combination group, and 35.3%, 39.1%, and 44.9% in the reserpine, clopamide, and nitrendipine groups, (*P*<0.0001). The reduction in SBP at week 6 in the combination group (–23.0 mm Hg) was greater compared to the reserpine, clopamide, and nitrendipine groups (–14.0, –13.6, and –11.6 mm Hg); *P* <0.001), resulting in rates of 62.7%, 45.6%, 40.6%, and 30.4% of patients achieving the goal SBP at week 6. Dose titration in those not achieving goal SBP by week 6 resulted in further SBP reductions in all groups except for the reserpine monotherapy group; and normalization was achieved at 12 weeks in 76.1% of the combination group compared with 44.1%, 46.4%, and 39.1% of the reserpine, clopamide, and nitrendipine groups compared to baseline. Secondary: Mean baseline heart rates were 74.9, 75.6, 75.2, and 73.8 beats per minute for the combination, reserpine, clopamide, and nitrendipine groups. Heart rate measurements remained constant in the clopamide and nitrendipine groups and fell in the reserpine and reserpine-clopamide groups by 5.6 and 5.3 beats per minute, by week 12.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The percentages of patients with one or more adverse events experienced by week 12 were almost the same in the combination group versus the reserpine and clopamide monotherapy groups (27% vs 28% and 29%), whereas the incidence of adverse events was 48% in the nitrendipine group (*P*=0.01). The numbers of patients withdrawing from the study due to adverse experiences were 2 (3%) each in the reserpine-clopamide group and reserpine groups, 5 (7%) in the clopamide group, and 9 (13%) in the nitrendipine group. Two serious events were investigator-determined as possibly drug related, resulting in study discontinuation; one in the clopamide group at 6 weeks (uterine bleeding) and one in the nitrendipine group at 12 weeks (tarry stools). The percentage of patients achieving goal DBP without an adverse events was 49% in the combination group, compared with 19%, 20%, and 12% in the reserpine, clopamide, and nitrendipine groups (*P*<0.0001). Body weight and electrocardiographic measurements did not change significantly in any group at 12 weeks compared to baseline.
Manyemba[19] HCTZ 25 mg QD plus reserpine 0.25 mg QD vs HCTZ 25 mg QD plus nifedipine SR 20 mg BID	OL, RCT, XO African American patients aged 21-65 years with hypertension (blood pressure >140/95 mm Hg) after 4 weeks of daily HCTZ therapy	N=32 10 weeks	Primary: The change in blood pressure from baseline to the end of each 4-week treatment period Secondary: Not reported	Primary: Reserpine reduced SBP by 15.9 mm Hg (95% CI, 8.4 to 23.4) and DBP by 11.1 mm Hg (95% CI, 7.5 to 14.6). Nifedipine SR reduced SBP by 18.9 mm Hg (95% CI, 12.1 to 25.7) and DBP by 9.6 mm Hg (95% CI, 7.2 to 12.0). There was no significant difference between the two groups (*P* values not reported). Secondary: Not reported
Materson et al[20] HCTZ 25 to 100 mg	DB, MC, RCT Men ≥60 years with	N=690 12 months	Primary: The average reduction in SBP,	Primary: A total of 269 patients were uncontrolled with HCTZ therapy alone and were randomized to receive hydralazine (n=68), methyldopa (n=71), metoprolol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD maintenance followed by: HCTZ 25 to 100 mg QD plus hydralazine 25, 50, or 100 mg BID vs HCTZ 25 to 100 mg QD plus methyldopa 250, 500, 1,000 mg BID vs HCTZ 25 to 100 mg QD plus metoprolol 50, 100, or 200 mg BID vs HCTZ 25 to 100 mg QD plus reserpine 0.05, 0.10, or 0.25 mg QD	hypertension not currently receiving antihypertensive therapy with a DBP 90-114 mm Hg and a SBP <240 mm Hg; or a DBP <100 mm Hg and a SBP <240 mm Hg if currently taking antihypertensive therapy and the blood pressure criteria was met after at least 2 weeks without medication		DBP, the number of patients achieving the goal blood pressure and the average change in heart rate Secondary: The rates of drug intolerances and incidence of adverse effects	(n=65), or reserpine (n=65). A total of 213 of the 269 patients achieved goal blood pressure with the addition of one of four therapies was added to HCTZ and entered the 6 month maintenance phase; 186 patients completed the maintenance phase. Across all 4 add-on therapies, there was an additional average reduction in blood pressure of 13.1/10.6 mm Hg. The average reduction in SBP (mm Hg)±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: –11.5±10.1 (*P*<0.001), –15.0±13.7 (*P*<0.001), –13.0±15.4 (*P*<0.001), and –12.7±11.5 (*P*<0.001), respectively. There was no statistically significant difference in SBP reductions among the different groups (*P*=0.43). The average reduction in DBP (mm Hg)±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: –11.3±5.9 (*P*<0.001), –10.6±6.3 (*P*<0.001), –10.6±6.7 (*P*<0.001), and –9.8±6.3 (*P*<0.001), respectively. There was no statistically significant difference in DBP reductions among the different groups (*P*=0.59). The average change in heart rate (beats per minute) ±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: 1.4±10.5 (*P*=NS), –1.6±9.3 (*P*=NS), 15.9±11.9 (*P*<0.05), and -7.9±10.7 (*P*<0.05), respectively. There was a statistically significant difference in change in heart rate among the different groups (*P*<0.001). The percentage of patients achieving the goal blood pressure at endpoint in the hydralazine, methyldopa, metoprolol, and reserpine groups was: 85.3%, 81.7%, 76.9%, and 72.3%, respectively (*P*=0.28). Secondary: Drug intolerance, defined as adverse effects prompting dose reduction or discontinuation, was present in 23.3% of those not achieving goal blood pressure compared with 2.8% of those achieving the goal blood pressure

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*P*<0.001). This was statistically significant in the hydralazine, methyldopa, and metoprolol groups, but not the reserpine group. There were 27 (10%) study terminations due to adverse drug events: hydralazine (n=3), methyldopa (n=8), metoprolol (n=9), and reserpine (n=7). There were 2 study terminations in the methyldopa-treated group and 1 in the reserpine group due to depression. The overall incidence of volunteered moderate or severe adverse effects, not prompting study termination was significantly greater (*P*<0.01) with methyldopa (31%) and hydralazine (25%) compared with reserpine (15%) or metoprolol (9%).
VA Medical Centers[21] Chlorthalidone 50 mg QD plus reserpine 0.25 mg QD vs chlorthalidone 50 mg QD plus reserpine 0.125 mg QD vs chlorthalidone 50 mg QD plus reserpine 0.05 mg QD vs chlorthalidone 25 mg QD plus reserpine	DB, MC, RCT Patients with mild to moderate hypertension who did not achieve normal blood pressure with chlorthalidone therapy alone	N=329 12 weeks	Primary: Changes in DBP and SBP readings and the percentage of patients achieving control at a DBP <90 mm Hg and at least 5 mm Hg below baseline Secondary: Side effects	Primary: The reduction in blood pressure (SBP/DBP) when reserpine was added to patient's chlorthalidone therapy averaged 11.0/10.4 mm Hg with chlorthalidone 50 mg plus reserpine 0.25 mg; 9.5/9.4 mm Hg with chlorthalidone 50 mg plus reserpine 0.125 mg; 6.4/8.5 mm Hg with chlorthalidone 50 mg plus reserpine 0.05 mg; and 9.9/9.6 mm Hg with chlorthalidone 25 mg plus reserpine 0.125 mg. The percentage of patients in whom control was achieved at DBP less than 90 mm Hg and at least 5 mm Hg below baseline with either chlorthalidone alone or in with reserpine was: 65% with chlorthalidone 50 mg plus reserpine 0.25 mg; 69% with chlorthalidone 50 mg plus reserpine 0.125 mg; 58% with chlorthalidone 50 mg plus reserpine 0.05 mg; and 56% with chlorthalidone 25 mg plus reserpine 0.125 mg. Secondary: Side effects of lethargy and impotence noted by patients with the 0.05 mg dose of reserpine were one third of the reports noted with the 0.25 mg dose. The incidence of other side effects did not differ.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
0.125 mg QD				
Psychotic States				
Berlant[22] Reserpine in combination with neuroleptics	RETRO Chronically disabled psychotic patients with symptoms refractory to lithium and neuroleptics	N=36 Duration not specified	Primary: The change in chronically persistent psychotic symptoms and functionality Secondary: Not reported	Primary: There was a moderate to dramatic response rate in 50% of the 36 chronically disabled psychotic patients with the addition of reserpine to neuroleptic and lithium therapies (*P* values not reported). The observed improvement was distinct compared to the baseline pattern of chronically persistent psychotic symptoms and poor functioning (*P* values not reported). Female patients and those with schizoaffective or bipolar disorders tended to respond best to treatment (*P* values not reported).

*Agent not commercially available in the United States (U.S.).
Drug regimen abbreviations: BID=twice daily, HCTZ=hydrochlorothiazide, QD=once daily, SR=sustained release
Study abbreviations: AC=active-controlled, CI=confidence interval, CT=controlled trial, DB=double blind, MC=multicenter, OL=open label, NS=not significant, PC=placebo-controlled, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, SB=single blind, XO=crossover
Miscellaneous abbreviations: DBP=diastolic blood pressure, SBP=systolic blood pressure, VA – Veterans Administration

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Peripheral Adrenergic Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
reserpine*	tablet	N/A	N/A	$

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

X. Conclusions

Reserpine, a peripheral adrenergic inhibitor, is Food and Drug Administration (FDA) approved for mild to moderate hypertension and agitated psychotic states.[3-4] The current hypertension guidelines do not recommend reserpine as initial therapy. Many of the current national guidelines do not address reserpine as an option for the treatment of hypertension, while some groups mention reserpine only as a therapeutic choice, but do not specifically make recommendations regarding its place in therapy. Reserpine is administered as a once-daily dosing regimen, which has proven efficacy for treating hypertension, with few significant drug interactions. Reserpine, however, has many adverse events, with depression, nasal congestion, and gastrointestinal symptoms observed.[2] Reserpine is not recommended as monotherapy for the treatment of hypertension and is generally used as adjunctive therapy in combination with thiazide diuretics, where it has been shown effective for treating hypertension.[2] In addition, reserpine is not specifically addressed in the psychiatric treatment guidelines. Reserpine is available generically.

Therefore, all brand products in this class review are comparable to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand peripheral adrenergic inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Miscellaneous Hypotensive Agents
AHFS Class 240892
September 10, 2008

I. Overview

Mecamylamine is classified by the American Hospital Formulary Service (AHFS) as a miscellaneous hypotensive agent and was one of the first oral antihypertensive agents, introduced in the mid-1950s.[1,2] Mecamylamine, a ganglionic blocker and secondary amine, inhibits acetylcholine at the autonomic ganglia. This causes blood vessel dilation and an increase in peripheral blood flow resulting in a decrease in blood pressure. Additionally, it blocks central nicotinic cholinergic receptors. Mecamylamine use has diminished due to its ganglionic side effects at antihypertensive doses.[2-4]

Table 1 lists the miscellaneous hypotensive agents that are included in this review. This review encompasses all dosage forms and strengths. Fenoldopam is administered primarily on an inpatient basis in institutions. Since it is not routinely dispensed in an outpatient pharmacy, it has not been included in this review.

Table 1. Miscellaneous Hypotensive Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
fenoldopam mesylate^	injection	Corlopam®*	none
mecamylamine	tablet	Inversine®	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the treatment of hypertension are listed in Table 2. The miscellaneous hypotensive agents are listed in the majority of treatment guidelines however; there are no specific recommendations for this drug. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Miscellaneous Hypotensive Agents

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[5]	• No specific recommendation is made concerning mecamylamine.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[6]	• No specific recommendation is made concerning mecamylamine.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[7]	• No specific recommendation is made concerning mecamylamine.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[8]	• No specific recommendation is made concerning mecamylamine.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[9]	• No specific recommendation is made concerning mecamylamine.
British Hypertension Society (BHS):	• No specific recommendation is made

Clinical Guideline	Recommendation(s)
Guidelines for Hypertension Management 2004 (BHS-IV)[10]	concerning mecamylamine.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[11]	• No specific recommendation is made concerning mecamylamine.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[12]	• No specific recommendation is made concerning mecamylamine.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[13]	• No specific recommendation is made concerning mecamylamine.

III. Indications

Food and Drug Administration (FDA)-approved indications for the miscellaneous hypotensive agents are listed 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 Miscellaneous Hypotensive Agents[3]

Generic Name	FDA-Approved Indications
Mecamylamine	Indicated for the management of moderately severe to severe essential hypertension and in uncomplicated cases of malignant hypertension.

IV. Pharmacokinetics

The pharmacokinetic parameters for miscellaneous hypotensive agents are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Hypotensive Agents[3]

Drug	Bioavailability (%)	Protein Binding (%)	Elimination	Half-Life (hours)	Active Metabolites
Mecamylamine	Not reported*	Not reported	Renal†	Not reported	Not reported

*It is noted that mecamylamine is "almost completely absorbed from the gastrointestinal tract". [3]
†Unchanged in the urine (alkalinization of the urine increases excretion, acidification of the urine reduces excretion). [3]

V. Drug Interactions

There are no reported drug interactions of major or moderate significance with the miscellaneous hypotensive agent, mecamylamine, although the package insert states that patients receiving antibiotics and sulfonamides generally should not be treated with ganglion blockers.[3,14] Additionally, the action of mecamylamine may be amplified by anesthesia, other antihypertensive agents, and alcohol. The mechanism of these interactions and specific drug agents are not specified.[3]

VI. Adverse Drug Events

The most common adverse reactions reported with the miscellaneous hypotensive agents are noted in Table 5.

Table 5. Adverse Events (%) Reported with the Miscellaneous Hypotensive Agents[3]

Adverse Events	Mecamylamine
Cardiovascular	
Orthostatic dizziness	✔
Postural hypotension	✔
Syncope	✔
Central Nervous System	

Adverse Events	Mecamylamine
Choreiform movements	✔
Convulsions	✔
Mental aberrations	✔
Paresthesias	✔
Tremor	✔
Gastrointestinal	
Anorexia	✔
Constipation	✔
Dryness of mouth	✔
Glossitis	✔
Ileus	✔
Nausea	✔
Vomiting	✔
Genitourinary	
Decreased libido	✔
Impotence	✔
Urinary retention	✔
Respiratory	
Fibrosis	✔
Interstitial pulmonary edema	✔
Other	
Blurred vision	✔
Dilated pupils	✔
Fatigue	✔
Sedation	✔
Weakness	✔

✔ Percent not specified.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous hypotensive agents are summarized in Table 6.

Table 6. Usual Dosing for the Miscellaneous Hypotensive Agents[3]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Mecamylamine	Initial: 2.5 mg twice daily (titrate in increments of 2.5 mg with at least 2 day intervals) Average: 25 mg daily, in 3 divided doses (some patients may respond to as little as 2.5 mg daily; however, some patients may require 2 to 4 doses or greater in severe cases when consistent control is difficult to achieve) Partial tolerance may develop, requiring daily dosage increases	Safety and effectiveness has not been established.	Tablet: 2.5 mg

VIII. Effectiveness

A thorough literature search from 1966 to the present failed to retrieve any clinical studies evaluating the safety and effectiveness of mecamylamine for the treatment of hypertension. The initial clinical trials were conducted in the 1950s. These trials established the drug's efficacy and side effect profile in patients with severe hypertension.[1]

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 7. Relative Cost of the Miscellaneous Hypotensive Agents

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
mecamylamine	tablet	Inversine®	$$$$$	N/A

N/A=not available.

X. Conclusions

Although the clinical literature reports that mecamylamine is effective for the management of moderate-to-severe hypertension, its clinical utility is minimal due to its adverse events profile and the availability of newer and more effective agents. Current hypertension treatment guidelines do not mention mecamylamine as a first-line or alternative agent for the treatment of hypertension.

Therefore, all brand products in this class review are comparable to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous hypotensive agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of α-Adrenergic Blocking Agents
AHFS Class 242000
September 10, 2008

I. Overview

Alpha-adrenergic blocking agents, also commonly referred to as α_1-blockers, competitively inhibit postsynaptic α_1-adrenergic receptors.[1] These receptors are classified into three subtypes: α_{1A}, α_{1B}, and α_{1D}.[2-4] They are located in the smooth muscle cell membrane of the peripheral blood vessels, as well as in various nonvascular smooth muscle and non-muscular tissues.[2-6] Since stimulation of the α_1 receptors in vascular smooth muscle leads to vasoconstriction of the blood vessels and resulting hypertension, α_1-blockers lower blood pressure by acting peripherally to dilate the blood vessels. Because α_1-adrenergic receptors are also found in the bladder neck, prostate capsule, and prostate fibromuscular stoma, α_1-blockers play a part in the treatment of benign prostatic hyperplasia.[5] Stimulation of the α_1 receptors in the urinary tract leads to increased urethral pressure and increased resistance to urine flow. Therefore, α_1-blockade causes rapid relaxation of smooth muscle tone which reduces the resistance to urine flow due to α-adrenergic tone.[5,7]

The most widely utilized guideline on the management of hypertension, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), does not recommend α_1-blockers as preferred first-line therapy.[8] In the previous report from this committee (JNC 6), α_1-blockers were considered effective as monotherapy in patients with certain comorbidities such as benign prostatic hyperplasia. However, that recommendation was changed in light of results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), where an α_1-blocker, doxazosin, was associated with a higher risk of stroke and incidence of combined cardiovascular disease events compared to the diuretic, chlorthalidone.[10]

The side-effect profile of α_1-blockers has also limited their role in the treatment of hypertension. α_1-Blockers can cause postural hypotension, reducing the standing systolic blood pressure by more than 10 milliliters of mercury (mm Hg). Syncope with sudden loss of consciousness can also occur, especially with the first few doses, rapid dose increases, or the addition of another antihypertensive drug to the treatment regimen. Other common adverse effects of α_1-blockers include headache and weakness.[11] However, unlike the diuretics and β-adrenergic blocking agents, α_1-blockers do not have an adverse effect on serum lipid levels. On the contrary, α_1-blockers have been shown to reduce total cholesterol by about 3 to 5 percent, and reduce triglyceride levels by 3 to 4 percent, and increase high-density lipoprotein cholesterol.[12] α_1-Blockers have also been shown to improve insulin sensitivity.[12]

α_1-Blockers are more commonly used to relieve the symptoms of benign prostatic hypertrophy (BPH). BPH is a condition characterized by nonmalignant enlargement of the prostate gland. BPH is associated with lower urinary tract symptoms (LUTS) such as frequent daytime urination, nocturia, a sensation of incomplete bladder emptying and a hesitant, weak, or intermittent urinary stream. BPH is rarely a life-threatening condition. Blockade of the receptors located at the bladder neck leads to relaxation of the urethra. This effect is beneficial in men with LUTS, but is harmful in women and may lead to stress or urge incontinence.[3]

Table 1 lists the α-adrenergic blocking agents included in this review. All agents are available generically in immediate-release formulations. The doxazosin sustained-release tablet (Cardura XL®) is not available generically; note that this formulation is not FDA indicated for the treatment of hypertension. This review encompasses all dosage forms and strengths.

Table 1. α-Adrenergic Blocking Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
doxazosin	sustained-release tablet, tablet	Cardura®*, Cardura XL®	doxazosin
prazosin	capsule	Minipress®*	prazosin

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
terazosin	capsule	Hytrin®*	terazosin

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the α-adrenergic blocking agents (α-blockers) are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the α-Adrenergic Blocking Agents

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[8]	• α_1-blockers may be useful in prostatism.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[13]	• α_1-Blockers may be useful in patients with prostatism.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[14]	• The use of α_1-blockers was not addressed in this guideline.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[15]	• The use of α_1-blockers was not addressed in this guideline.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[16]	• If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-adrenergic blocking agent (β-blocker) or a selective α_1-blocker.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[17]	• The use of α_1-blockers was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[18]	• The use of α_1-blockers was not addressed in this guideline.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[19]	• The use of α_1-blockers was not addressed in this guideline.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[20]	• The use of α_1-blockers was not addressed in this guideline.
American Urological Association (AUA): **AUA Guideline on Management of Benign Prostatic Hyperplasia (BPH) (2003)**[21]	<u>Mild Symptoms of BPH</u> • A period of physician monitoring and no active intervention ("watchful watching") is recommended for patients with mild symptoms of BPH (AUA symptom score ≤ 7) and patients with moderate or severe symptoms (AUA symptom score ≥ 8) who are not bothered by their symptoms or who have not yet developed complications of BPH (e.g., renal insufficiency, urinary retention, or recurrent infection).

Clinical Guideline	Recommendation(s)
	Moderate-to-Severe Symptoms of BPH • Drug and procedural therapeutic options exist for patients with bothersome moderate to severe symptoms. • Drug treatments options include α_1-blockers and α-reductase inhibitors. • The guidelines consider the four long-acting α_1-blockers, alfuzosin, doxazosin, tamsulosin, and terazosin, to have equal clinical effectiveness. • The α-reductase inhibitors are considered for patients with bothersome symptoms and demonstrable prostatic enlargement. • α-reductase inhibitors may also be considered for patients with symptomatic prostatic enlargement without bothersome symptoms to prevent progression of the disease. • Combination therapy with an α_1-blocker plus an α-reductase inhibitor may also be considered for patients with bothersome symptoms and demonstrable prostatic enlargement.

III. Indications

Food and Drug Administration (FDA)-approved indications for the α-adrenergic blocking agents are listed 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 α-Adrenergic Blocking Agents[11,23-26]

Indication	Doxazosin	Prazosin	Terazosin
Hypertension	✔ *	✔ †	✔ †
Benign prostatic hyperplasia	✔		✔

*Immediate-release formulation only; alone or in combination with diuretics, β-adrenergic blocking agents, calcium-channel blocking agent or angiotensin-converting enzyme inhibitors. Product information for Cardura XL® states that it is not indicated for the treatment of hypertension.
†Alone or in combination with other antihypertensive drugs.

IV. Pharmacokinetics

The pharmacokinetic parameters for the α-adrenergic blocking agents are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the α-Adrenergic Blocking Agents[22-24,26]

Drug	Bioavailability (%)	Protein Binding (%)	Active Metabolites	Elimination	Half-Life (hours)
Doxazosin	65 54-59 (SR)*	98	Several metabolites, activity unknown	Urine (9%) Feces (63%)	9-22 15-19 (SR)
Prazosin	48-68	92-97	*o*-demethylated metabolites	Urine (3%-4%) Rest via bile and Feces; 75%-80% as metabolites	2-3
Terazosin	90	90-94	Several metabolites, activity not reported	Urine (40%) Feces (20%)	9-12

Sr=sustained-release formulation.
*Relative to the immediate-release formulation.

V. Drug Interactions

Table 5 summarizes the significant drug interactions with the α-adrenergic blocking agents (α-blockers).

Table 5. Significant Drug-Drug Interactions with the α-Adrenergic Blocking Agents[11]

Drug(s)	Significance Level	Interaction	Mechanism
α_1-Blockers (doxazosin, prazosin, terazosin	2	Ethanol	Possible inhibition of the sympathetic nervous system by the α-blockers may accentuate alcohol-induced hypotension.
α_1-Blockers (doxazosin, prazosin, terazosin	2	Tadalafil	Unknown mechanism. Blood pressure lowering effect of the α-blockers may be increased.
α_1-Blockers (doxazosin, prazosin, terazosin	2	Vardenafil	Additive or synergistic pharmacologic action, increasing the risk of hypotension.
Prazosin	2	β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carteolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Unknown mechanism. Postural hypotension may be increased with concurrent therapy.
Prazosin	2	Verapamil	Unknown mechanism. Verapamil may increase serum prazosin concentration and increase sensitivity to prazosin-induced postural hypotension.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

α-Adrenergic blocking agents (α-blockers) can cause marked hypotension (especially postural hypotension) and syncope with sudden loss of consciousness with the first few doses. This "first-dose" effect can be minimized by administration of the first dose at bedtime. Hypotension and syncope can also occur with dose increases, addition of other antihypertensives, and therapy interruptions. The elderly are more at risk for this adverse reaction. Other adverse reactions associated with α-blockers are listed in Table 6 below.[16-20]

Table 6. Adverse Drug Events (%) Reported with the α-Adrenergic Blocking Agents[23-26]

Adverse Event	Doxazosin	Prazosin	Terazosin
Cardiovascular			
Arrhythmia	1	-	-
Chest pain	1-2	-	-
Edema	3-4	1-4	-
Flushing	1	-	-
Hypotension	1-2	-	-
Palpitations	1-2	5	1-4
Postural hypotension	1-2	1-4	1-4
Syncope	-	1-4	-
Tachycardia	-	-	2
Central Nervous System			
Anxiety	-	-	-
Asthenia	1-7	-	7-11
Ataxia	-	-	-
Depression	1	1-4	-
Dizziness	5-19	10	9-19

Adverse Event	Doxazosin	Prazosin	Terazosin
Drowsiness	-	8	-
Fatigue	8-12	-	-
Headache	5-14	8	5-16
Hypertonia	1	-	-
Insomnia	1	-	-
Kinetic disorders	1	-	-
Lack of energy	-	7	-
Nervousness	2	1-4	2
Paresthesia	1	-	3
Somnolence	1-5	-	4-5
Vertigo	2-4	1-4	1
Weakness	-	7	-
Dermatological			
Rash	1	1-4	-
Pruritus	1	-	-
Gastrointestinal			
Abdominal pain	2	-	-
Constipation	1	1-4	-
Diarrhea	2	1-4	-
Dry mouth	2	1-4	-
Dyspepsia	1-2	-	-
Flatulence	1	-	-
Nausea	1-3	5	2-4
Vomiting	-	1-4	-
Genitourinary			
Impotence	1	-	1-2
Polyuria	2	-	-
Sexual dysfunction	1	-	-
Urinary frequency	-	1-4	-
Urinary incontinence	1	-	-
Urinary tract infection	1	-	1
Musculoskeletal			
Arthralgia/arthritis	1	-	-
Back pain	2-3	-	2
Muscle cramps	1	-	-
Muscle weakness	1	-	-
Myalgia	1	-	-
Respiratory			
Dyspnea	1-3	1-4	2-3
Epistaxis	1	1-4	-
Nasal congestion	-	1-4	2-6
Respiratory disorder	1	-	-
Respiratory tract infection	5	-	-
Rhinitis	3	-	-
Sinusitis	-	-	3
Miscellaneous			
Blurred vision	-	1-4	2
Blurred vision/amblyopia	-	-	1
Conjunctivitis/eye pain	1	-	-
Face edema	1	-	-
Influenza-like symptoms	1	-	2
Pain	2	-	-

Adverse Event	Doxazosin	Prazosin	Terazosin
Pain in extremities	-	-	4
Peripheral edema	-	-	1-6
Sclera reddened	-	1-4	-
Sweating increased	1	-	-
Tinnitus	1	-	-
Vision abnormal	1-2	-	-

- Event not reported or incidence <1%.
✓ Percent not specified.

VII. Dosing and Administration

The usual dosing regimens for the α-adrenergic blocking agents (α-blockers) are summarized in Table 7. Treatment with α-blockers should be initiated at bedtime and at the lowest dose to minimize the likelihood of the "first-dose" effect. Dosages should be titrated up slowly to achieve the desired response. If therapy is interrupted for more than a few days, the initial dosing regimen and titration schedule should be reinstituted. Other antihypertensive agents should be added cautiously to reduce the risk of developing significant hypotension.

Table 7. Usual Dosing for the α-Adrenergic Blocking Agents[23-26]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose†	Availability
Doxazosin	Hypertension: IR: Initial: 1 mg once daily Maintenance: 1 to 16 mg once daily Maximum: 16 mg/day Benign Prostatic Hyperplasia: IR: Initial: 1 mg once daily Maintenance: 1 to 8 mg once daily Maximum: 8 mg/day SR: Initial dose: 4 mg once daily, administered with breakfast Maintenance dose: 4 to 8 mg daily Maximum: 8 mg/day	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 4 mg 8 mg Sustained-release (SR) tablet: 4 mg 8 mg
Prazosin	Hypertension: Initial: 1 mg/dose 2 to 3 times a day Maintenance: 3 to 15 mg/day in 2 to 4 divided doses Maximum: 40 mg/day	Safety and efficacy in children have not been established.	Capsule: 1 mg 2 mg 5 mg
Terazosin	Hypertension: Initial : 1 mg at bedtime Maintenance: 1 to 20 mg once daily Maximum: 20 mg/day Benign Prostatic Hyperplasia: Initial: 1 mg at bedtime Maintenance: 1 to 10 mg/day Maximum: 20 mg/day	Safety and efficacy in children have not been established.	Capsule: 1 mg 2 mg 5 mg 10 mg

IR=immediate-release, SR=sustained-release

VIII. Effectiveness

The role of α-adrenergic blocking agents (α-blockers) in the treatment of hypertension has been largely defined by two major trials, TOMHS and ALLHAT.[10,33-36] Both of these landmark trials compared the effectiveness of several classes of antihypertensive agents. α_1-Blockers have been shown to be effective in lowering blood pressure in numerous studies. However, prior to the ALLHAT study, there was no data regarding the effects of α_1-blockers on morbidity (e.g., congestive heart failure risk reduction) and mortality. Clinical studies evaluating the safety and efficacy of the α-adrenergic blocking agents are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the α-Adrenergic Blocking Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypertension				
Hayduk, Schneider, et al[27] Doxazosin 1 to 16 mg QD vs terazosin 1 to 20 mg QD	DB, MC, RA Patients with high blood pressure	N=55 14 weeks	Primary: Blood pressure (success defined as decrease in standing DBP to <90 mm Hg and by 5 mm Hg or at least a 10 mm Hg reduction in standing DBP; normalized blood pressure defined by DBP ≤90 mm Hg) Secondary: Not reported	Primary: Therapeutic success was higher in the doxazosin treated group compared with the terazosin treated group (73% vs 64%; *P* value not reported). At endpoint, there were more subjects with normalized blood pressure in the doxazosin group compared with the terazosin group (65% vs 57%; *P* value not reported). The incidence of treatment-related side effects was higher in terazosin group compared with the doxazosin group (39% vs 30%; *P* value not reported). Secondary: Not reported
Torvik et al[28] Doxazosin 1 to 16 mg QD vs prazosin 0.5 to 10 mg BID vs placebo	DB Patients with essential hypertension	N=172 12 weeks	Primary: Blood pressure, heart rate, plasma lipid profiles Secondary: Not reported	Primary: Doxazosin and prazosin both produced significant reductions in blood pressures compared with placebo ($P<0.05$ to $P<0.005$). There was no significant difference between the three groups in plasma lipid profiles or heart rate (*P* value not reported). There was a significant decrease in triglycerides from baseline in the doxazosin treated group only ($P<0.05$). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fukiyama et al[29] Doxazosin vs prazosin	DB, MC, RA Patients with essential hypertension	N=126 12 weeks	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: There was no significant difference between the groups in blood pressure reduction (*P*=0.7826). Both drugs produced significant decreases in blood pressure from baseline (*P*<0.001). No significant changes in heart rate were observed (*P* value not reported). Secondary: Not reported
DePlanque[30] Doxazosin QD vs prazosin BID	DB, DD, PG Patients with mild or moderate essential hypertension not adequately controlled by diuretics and β-blockers	N=43 14 weeks	Primary: Blood, heart rate, serum lipid levels, calculated coronary heart disease risk using the Framingham equation Secondary: Not reported	Primary: There was no statistically significant difference between the groups in SBP (*P*=NS), heart rate (*P*=NS), or serum lipid levels (*P* value not reported). Doxazosin showed a significantly greater reduction in standing (*P*=0.01) and supine (*P*=0.04) DBP compared with prazosin. 84.2% of the doxazosin treated group and 56.5% of the prazosin treated group achieved therapeutic success (*P* value not reported). Doxazosin (*P*=0.02) showed a greater reduction from baseline in the calculated risk of coronary heart disease than prazosin (*P*=NS). Secondary: Not reported
Deger[31] Prazosin BID vs terazosin QD vs placebo	DB, MC, PC Patients with mild to moderate hypertension	N=174 14 weeks	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: Terazosin produced significant reduction in supine and standing DBP when compared to placebo (*P*≤0.05). Prazosin did not produce a significant reduction in supine DBP, but did produce a significant reduction in mean standing DBP when compared to placebo (*P* value not reported). There was no significant difference in heart rate changes between the treatment groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Ruoff[32] Study 1: Prazosin vs terazosin vs placebo Study 2: terazosin vs HCTZ Study 3: terazosin and HCTZ vs prazosin and HCTZ	DB, PG, RA Patients with mild to moderate hypertension	Study 1 N=54 Study 2 N=37 Study 3 N=28	Primary: Blood pressure, pulse rate, body weight, laboratory tests, physical examinations, electrocardiograms Secondary: Not reported	Primary: Study 1- There was no significant difference in blood pressure changes between the terazosin and prazosin treatment groups (*P* value not reported). Study 2- HCTZ produced a significantly greater reduction in supine DBP compared with terazosin (*P* value not reported). There were no significant differences in standing blood pressure between the HCTZ and terazosin treatment groups (*P* value not reported). Study 3- There were no significant differences in blood pressure between the treatment groups (*P* value not reported). The drug treatments did not produce significant changes in pulse rates, body weights, laboratory test results, physical examinations, or electrocardiograms (*P* value not reported). Secondary: Not reported
ALLHAT[3,33,34] Doxazosin 2 to 8 mg QD vs chlorthalidone 12.5 to 25 mg QD	AC, DB, RA Subjects ≥55 years of age with hypertension and had at least one cardiac risk factor	N=24,335 3.3 years	Primary: Combined occurrence of fatal coronary heart disease or nonfatal myocardial infarction Secondary: All-cause mortality, stroke, combined CVD	Primary: There was no difference in risk of fatal coronary heart disease or nonfatal myocardial infarction (*P*=0.71) or total mortality (*P*=0.56) between the chlorthalidone and doxazosin treatment group. Secondary: The doxazosin group compared with the chlorthalidone group had a higher risk of stroke (RR, 1.19; 95% CI, 1.01 to 1.40; *P*=0.04) and combined CVD (RR, 1.25; 95% CI, 1.17 to 1.33; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Congestive heart failure risk was doubled in the doxazosin group compared with the chlorthalidone group (*P*<0.001), and the RR was 1.16 (*P*<0.001) for angina, 1.15 (*P*=0.05) for coronary revascularization, and 1.07 (*P*=0.50) for peripheral arterial disease. Mean SBP in the doxazosin group was about 2 to 3 mm Hg higher than in the chlorthalidone group, while the mean DBP was the same (*P* value not reported). There was a greater reduction in SBP in those treated with chlorthalidone compared with doxazosin (*P*<0.01 in patients with newly diagnosed with diabetes or with no glucose disorder; *P*=NS for patients with known diabetes). The doxazosin group compared with the chlorthalidone group had an increased heart failure risk (RR, 1.85; 95% CI, 1.56 to 2.19 in patients with known diabetes mellitus and RR, 1.63; 95% CI, 1.05 to 2.55 in the patients with newly diagnosed glucose disorder).
Neaton et al[35] TOMHS Doxazosin 2 to 4 mg QD vs chlorthalidone 15 to 30 mg QD vs acebutolol 400 mg QD vs	DB, MC, PC, RA Patients with mild hypertension (DBP <100 mm Hg)	N=902 4.4 years	Primary: Outcome measures: blood pressure, quality of life, side effects, blood lipid levels and analysis of other serum components, echocardiographic changes, and incidence of cardiovascular events Secondary: Not reported	Primary: There was a significant reduction in blood pressure in all the active treatment groups compared with placebo (–15.9 vs –9.1 mm Hg for SBP and –12.3 vs –8.6 mm Hg for DBP; *P*<0.0001). There were no major differences in blood pressure lowering between the 5 active treatment groups (*P*=0.10). Total cholesterol was significantly reduced more in the doxazosin group than in the amlodipine, chlorthalidone, and placebo groups (*P*<0.01). The reduction in LDL-C was significantly more in doxazosin group than in the amlodipine, chlorthalidone, and placebo groups. Reduction in triglycerides was significantly larger with the doxazosin, enalapril, and amlodipine groups than acebutolol group (*P*<0.01). The lowest level of fasting insulin was observed with doxazosin (*P* value not reported); fasting insulin was lower than placebo in all drug groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amlodipine 5 mg QD vs enalapril 5 to 10 mg QD vs placebo				Secondary: Not reported
Liebson et al[36] TOMHS Doxazosin in addition to nutritional-hygienic intervention (reduction in weight, dietary sodium, and alcohol consumption and increase physical activity) vs chlorthalidone vs acebutolol vs amlodipine vs	DB, PC, RA Patients with mild hypertension	N=844 4 years	Primary: Changes in blood pressure and pulse, changes in left ventricular mass from baseline to end of study period as assessed by echocardiograms Secondary: Not reported	Primary: All drug treatment groups showed significantly greater reduction of blood pressure compared with placebo (mean decrease of 16/12 vs 9/9 mm Hg; $P<0.001$). Pulse rate decreased by 10 bpm for the acebutolol group compared with 1 to 3 bpm for the other treatment groups (*P* value not reported). All drug treatment groups and the placebo group showed significant decreases (10% to 15%) in left ventricular mass. The chlorthalidone group showed the largest decrease in left ventricular mass at 34 g compared to 24 to 27 g for the other treatment groups (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enalapril vs placebo				
Dahlöf et al[37] ASCOT-BPLA Amlodipine 5 to 10 mg and if needed perindopril 4 to 8 mg or atenolol 50 to 100 mg and if needed bendroflumethiazide 1.25 to 2.5 mg If goal blood pressure was still not achieved, doxazosin 4 to 8 mg was added to the regimen.	CON, MC, RA Patients with hypertension	N=19,257 5.5 years	Primary: Nonfatal myocardial infarction and fatal coronary heart disease Secondary: Nonfatal myocardial infraction, and fatal coronary heart disease, total coronary endpoint, total cardiovascular events and procedures, all-cause mortality, cardiovascular mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, silent myocardial infarction, unstable angina, chronic stable angina, peripheral arterial disease, life-threatening arrhythmias, development of diabetes mellitus, development of renal impairment	Primary: The trial was halted early due to findings that patients on the amlodipine-perindopril regimen had fewer of the primary endpoints (P=0.1052) and lower rates of fatal and nonfatal stroke (P=0.0003), total cardiovascular events and procedures (P<0.0001), all-cause mortality (P=0.025), and incidence of developing diabetes (P<0.0001). There was a greater reduction in blood pressure by an average of 2.7/1.9 mm Hg in the amlodipine-based regimen compared with the atenolol-based regimen (P value not reported). There was no significant difference in the percent of patients (25%) that stopped therapy because of an adverse event between the two treatment groups (P value not reported). However, a significantly greater proportion of patients in the amlodipine-based regimen stopped the trial therapy early because of serious adverse events compared with the atenolol-based regimen (P<0.0001). Secondary: Patients on the amlodipine-perindopril regimen had fewer fatal and nonfatal strokes (P=0.0003), total cardiovascular events and procedures (P<0.0001), and all-cause mortality (P=0.025). Patients on the amlodipine-perindopril regimen had less chance of developing diabetes (P<0.0001).
Brown et al[38] Study A: Doxazosin followed by	DB, RA, TW, XO Patients with moderate or severe	N=24 18 weeks	Primary: Blood pressure and heart rate, foot volume as measure of edema,	Primary: Study A: The decrease in blood pressure was significantly greater than the sum of the blood pressure falls at the end of the single drug treatment periods (P value

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amlodipine followed by doxazosin and amlodipine vs Study B: enalapril followed by amlodipine followed by enalapril and amlodipine	hypertension		plasma noradrenaline concentration Secondary: Not reported	not reported). The reduction in blood pressure was greater with amlodipine than doxazosin (*P*<0.01). The reduction in blood pressure was greater with combination than amlodipine (*P*<0.001). No significant changes in heart rate (*P* value not reported) were observed. One subject developed ankle edema. The plasma noradrenaline concentration did not change significantly during the single drug treatment periods, but doubled at the end of the combination treatment period (*P*<0.05). Study B: The reduction in blood pressure was significantly greater with amlodipine than enalapril (*P*<0.05). The reduction in blood pressure was significantly greater with combination than amlodipine (*P*<0.05) with the exception of erect blood pressure (*P* value not reported). No significant changes in heart rate were noted (*P* value not reported). No significant difference in foot volume was observed between treatments (*P* value not reported). The plasma noradrenaline was significantly higher than at baseline (*P*<0.01). Secondary: Not reported
Deary et al[39] Doxazosin 1 to 4 mg vs amlodipine 5 mg vs lisinopril 2.5 to 10 mg vs	DB, LSR, XO Hypertensive patients, aged 18 to 55 years old	N=34 42 weeks (6 week treatment of each drug or placebo, then the 7th week was a repeat of each patient's most effective, tolerated drug)	Primary: Blood pressure and heart rate Secondary: Not reported	Primary: All drug treatments caused significant decreases in blood pressure (*P* values not reported). Bendroflumethiazide performed significantly worse (*P*=0.0016) and bisoprolol performed significantly better (*P*=0.004) than amlodipine. When the most effective drugs for each patient were tabulated, all drugs included in the study except for bendroflumethiazide, were represented. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
bisoprolol 5 mg vs bendroflumethiazide 2.5 mg vs placebo				
Hayduk[40] Study 1: Doxazosin 1 to 16 mg QD vs prazosin 1 to 20 mg BID vs HCTZ 25 to 100 mg QD vs nadolol 40 to 160 mg QD vs atenolol 50 to 100 mg QD vs	Study 1: DB, MC Study 2: DB Patients with hypertension	Study 1: N=903 10 to 24 week trial; therapy continued for up to 62 weeks Study 2: N=52 12 weeks	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: Blood pressure lowering effect of doxazosin was similar to that of the other antihypertensive drugs (*P* value not reported). There was no significant difference in the heart rate with the doxazosin treated group (*P* value not reported). The β-blockers demonstrated clinically significant bradycardia (*P* value not reported). Both doxazosin and terazosin were equally efficacious, but doxazosin was effective at significantly lower doses (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metoprolol 100 to 200 mg BID vs placebo Study 2: doxazosin 16 mg QD vs terazosin 20 mg QD				
Trost et al[41] Doxazosin 1 to 16 mg QD vs HCTZ 25 to 100 mg QD	DB, MC, PG Patients with hypertension	N=104 6 months	Primary: Blood pressure and serum lipid changes Secondary: Not reported	Primary: There was no significant difference in the supine and standing blood pressures between the two treatment groups (*P* value not reported). There was significantly greater reduction in total triglyceride (*P*=0.002) and total cholesterol concentration (*P*=0.006) and significantly greater increase in HDL-C:total cholesterol ratio (*P*=0.001) in the doxazosin arm compared with the HCTZ arm. Secondary: Not reported
Grimm et al[42] Doxazosin 2 to 16 mg vs HCTZ 25 to 50 mg	DB, PG, RA Patients with hypertension	N=107 1 year	Primary: Blood pressure, heart rate, biochemistries, lipids/lipoproteins, QOL, echocardiograms, adverse effects Secondary: Not reported	Primary: There were no significant differences in blood pressure lowering, heart rate, QOL measures, or serious adverse effects between the two treatment groups (*P* value not reported). The doxazosin treated group experienced a more favorable high density lipoprotein /total cholesterol ratio ($P \leq 0.01$) compared with the hydrochlorothiazide group. Both drug treatments showed significant reduction in left ventricular mass ($P<0.001$) and wall thickness ($P<0.05$). The left ventricular systolic and diastolic internal dimensions were significantly less in the HCTZ group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared with the doxazosin group (*P* value not reported). Secondary: Not reported
Ferrara et al[43] Doxazosin 1 to 16 mg QD vs captopril 25 to 150 mg QD	MC, OL, PG Patients with hypercholesterolemia and hypertension	N=224 14 weeks	Primary: Blood pressure (normalized blood pressure defined as standing diastolic pressure ≤ 90 mm Hg), serum lipid levels, quality of life Secondary: Not reported	Primary: Blood pressure was significantly reduced with both drugs ($P<0.001$). 73% of the doxazosin group and 67% of the captopril group achieved normalized blood pressure (*P* value not reported). Serum total cholesterol level was significantly improved with both drugs ($P<0.001$). The HDL-C concentration was only significantly increased in the doxazosin group ($P<0.001$). The calculated 10-year risk for the development of coronary heart disease was significantly reduced with both drug treatments ($P<0.001$). Secondary: Not reported
Derosa et al[44] Doxazosin 4 mg QD vs irbesartan 300 mg QD	DB, PG, RA Patients with type 2 diabetes and mild hypertension	N=96 1 year	Primary: Blood pressure, glucose metabolism and lipid parameters Secondary: Not reported	Primary: Blood pressure was significantly reduced in both treatment groups compared with baseline ($P<0.01$). Irbesartan was significantly better in lowering blood pressure compared to doxazosin ($P<0.05$). Doxazosin significantly reduced glycosylated hemoglobin, fasting plasma glucose, fasting plasma insulin, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides ($P\leq0.05$ for all parameters). As monotherapy, neither of the drugs achieved adequate blood pressure control. Secondary: Not reported
Taylor et al[45]	DB, PG	N=67	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Doxazosin 1 to 16 mg QD vs enalapril 10 to 40 mg QD	Patients with mild or moderate essential hypertension	18 weeks	Blood pressure (therapeutic success defined as standing DBP ≤90 mm Hg), lipid parameters Secondary: Not reported	74% of the doxazosin group achieved therapeutic success compared with 81% of the enalapril group (*P* value not reported). Blood pressures were significantly reduced in both groups (*P* value not reported). There were no significant changes in the lipid profile observed for either drug (*P* value not reported). Secondary: Not reported
Wessels[46] Doxazosin QD vs enalapril QD	DB, DD, PC, RA Patients with mild or moderate essential hypertension	N=54 12 weeks	Primary: Blood pressure, heart rate, serum lipid profile, calculated coronary heart disease risk Secondary: Not reported	Primary: Both drugs produced significant reductions in blood pressure ($P<0.05$). There was no significant change in heart rate with both drugs (no *P* value reported). Doxazosin showed a significant reduction in the total serum cholesterol concentration ($P<0.05$). Doxazosin also showed a decrease in triglyceride level (*P*=NS) and an increase in HDL-C/total cholesterol ratio (*P*=NS). Coronary heart disease risk reduction was significant and greater in the doxazosin group compared with the enalapril group (–27.58% vs –18.49%, $P<0.02$). Secondary: Not reported
Hjortdahl et al[47] Doxazosin QD vs HCTZ QD	DB, RA Patients with mild to moderate essential hypertension	N=115 24 weeks	Primary: Blood pressure, heart rate, lipid profile, and side effects Secondary: Not reported	Primary: There was no significant difference between treatment groups for blood pressure and heart rate (*P* value not reported) except HCTZ produced significantly greater supine SBP than doxazosin ($P=0.04$). There were significant reductions in total cholesterol ($P=0.006$) and total triglycerides ($P=0.018$) for the doxazosin group. 11 patients of the HCTZ group had an abnormally low potassium level and 7 of the HCTZ treated group had abnormally high uric acid concentrations.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Ott et al[48] Doxazosin 1 to 16 mg QD vs atenolol 50 to 100 mg QD	DB, MC, RA Patients with mild to moderate hypertension	N=126 20 weeks	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: There was no significant difference between treatment groups in blood pressure (*P* value not reported). Both drugs reduced heart rate, but atenolol produced a significantly greater decrease in heart rate than doxazosin ($P<0.001$). Secondary: Not reported
Frick et al[49] Doxazosin 1 to 16 mg QD vs atenolol 50 to 100 mg QD	DB, DD, MC, RA Patients with mild to moderate essential hypertension	N=152 1 year	Primary: Blood pressure, heart rate, lipid profile Secondary: Not reported	Primary: At endpoint, there was greater blood pressure reduction with atenolol than doxazosin. This was statistically significant only in the supine position ($P<0.05$). Doxazosin reduced the heart rate slightly, while atenolol produced a marked bradycardia ($P<0.0001$). High density lipoprotein /total cholesterol ratio was raised in the doxazosin group and lowered in the atenolol group ($P=0.001$). Triglyceride levels decreased in the doxazosin group and increased in the atenolol group (–5.0% vs +42.7%; $P<0.001$). Secondary: Not reported
Daae et al[50] Doxazosin QD vs atenolol QD	DB, MC, PG Patients with mild to moderate hypertension	N=228 1 year followed by a 4-year open-label extension phase	Primary: Blood pressure, heart rate, lipid profile, calculated risk of developing coronary heart disease in ten years using the Framingham equation Secondary:	Primary: Both groups showed similar decreases in blood pressure (*P* value not reported). The doxazosin-treated group had a significantly greater reduction from baseline in coronary heart disease risk than the atenolol-treated group ($P<0.05$). Total cholesterol significantly decreased from baseline in both treatment groups ($P\leq0.05$), with no statistically significant difference between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	groups (no *P* value reported). HDL–C (*P*<0.01), the HDL-C:total cholesterol ratio (*P*<0.01), and triglyceride levels (*P*<0.01) significantly improved in the doxazosin group compared with the atenolol group. Secondary: Not reported
Talseth et al[51] Doxazosin (mean dose used: 5.2 mg QD) vs atenolol (mean dose used: 66.4 mg QD)	PG, RA Patients with mild and moderate hypertension	N=164 3 years	Primary: Blood pressure, heart rate, lipids profile, calculated coronary heart disease risk using the Framingham equation Secondary: Not reported	Primary: Both drugs produced similar reductions in blood pressure (*P* value not reported). Atenolol produced a significant decrease in heart rate (*P*<0.05), while doxazosin did not change the heart rate significantly (*P* value not reported). Doxazosin significantly reduced triglyceride levels (*P*<0.001), increased HDL-C levels (*P*<0.001), and increased the HDL-C:total cholesterol ratio (*P*<0.001) compared with atenolol. The calculated coronary heart disease risk was significantly increased with atenolol (*P*<0.05) and significantly decreased with doxazosin (*P*<0.05) from baseline. Secondary: Not reported
Carruthers et al[52] Doxazosin QD vs atenolol QD	COMP, RA Patients with mild to moderate systemic hypertension and normal serum lipid	N=191 24 weeks	Primary: Calculated coronary artery disease risk using the Framingham formula Secondary: Not reported	Primary: Doxazosin treatment produced a significantly greater reduction in coronary heart disease risk compared with atenolol (*P*=0.0074). The relative risk of coronary heart disease was reduced to 0.92 in the atenolol group (*P*=0.144) and 0.74 in the doxazosin group (*P*=0.0001) from baseline. Secondary: Not reported
Searle et al[53] Doxazosin 11 mg (mean dose) QD and	DB, MC, RA Patients with mild to moderate	N=87 12 weeks	Primary: Blood pressure reduction, heart rate change, change in	Primary: Blood pressure significantly decreased in the atenolol-doxazosin–treated group compared with the atenolol-placebo–treated group (17.0/12.3 vs 6.2/6.7 mm Hg; *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atenolol 100 mg QD vs placebo and atenolol 100 mg QD	essential hypertension		serum lipids Secondary: Not reported	The supine blood pressure was decreased by 13.2/9.8 mm Hg in the atenolol-doxazosin–treated group compared with 9.2/6.0 mm Hg in the atenolol-placebo–treated group (*P*=NS). Only minor, insignificant changes in serum lipids and no significant changes in heart rate were observed between the treatment groups (*P* value not reported). Secondary: Not reported
Ohta et al[54] Doxazosin 1 to 2 mg QD to BID added to combination of calcium channel blockers and angiotensin II receptor blocker or angiotensin converting enzyme inhibitors	RETRO Hypertensive patients that showed poor blood pressure control	N=41 3 months (mean follow-up 170 days)	Primary: Blood pressure, blood chemistry Secondary: Not reported	Primary: Blood pressure decreased from 152±14/81±12 to 135±14/70±11 mmHg after the addition of doxazosin at a mean dose of 1.5 mg/day (*P*<0.001). When good SBP control was defined as <140 mm Hg, the prevalence of patients with good SBP control increased from 24% to 61% (*P*<0.01). Similarly, the prevalence of patients with good DBP control (<90 mm Hg) increased from 78% to 98% (*P*<0.01). Patients whose SBP decreased more than 10 mm Hg (n=25) showed significantly higher baseline SBP, serum total cholesterol and low-density lipoprotein cholesterol levels compared to those who showed less SBP reduction (<10 mm Hg; *P*<0.01). Comparable blood pressure reductions were obtained between obese patients (body mass index ≥25, change in blood pressure (Δ blood pressure) at 3 months: -15±15/-12±9 mm Hg, n=18) and nonobese patients (BMI<25, Δ blood pressure: -14±19/-7±8 mm Hg, n=23) patients. Secondary: Not reported
de Alvaro et al[55] ASOCIA	MC, PRO, NC Patients with hypertension	N=3,631 16 weeks	Primary: Goal blood pressure (<140/<90 mm Hg), adverse events	Primary: The proportion of patients reaching goal (<140/<90 mm Hg) after 4 weeks of add-on therapy with doxazosin GITS was 39% and increased to 61% at Week 16. SBP and DBP (mean ± SEM) decreased, respectively, from 161.6

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Doxazosin GITS 4 mg QD Added to entry medication Increased to 8 mg QD at Week 4 in cases of inadequate blood pressure control	(≥140/≥90 mm Hg) on previous antihypertensive medication that was uncontrolled		Secondary: Not reported	± 0.2 and 95.1 ± 0.1 mm Hg at baseline to 142.2 ± 0.2 and 84.1 ± 0.1 mmHg at Week 4 (*P*<0.0001) and 136.8 ± 0.2 and 80.6 ± 0.2 mm Hg at Week 16 (*P*<0.0001). Adverse events occurred in 108 patients (3.0%), with 57 (1.6%) related to the study treatment. In 17 patients (0.5%), serious adverse events were described, but only one was related to the study drug. Secondary: Not reported
Wright et al[56] ALLHAT Doxazosin vs chlorthalidone vs amlodipine vs lisinopril	RA, DB Hypertensive individuals with and without MetS	N=42,418 3.2 years (median follow-up)	Primary: Fatal coronary heart disease or nonfatal myocardial infarction Secondary: Heart failure, combined CVD, stroke, end-stage renal disease	Primary: No differences were noted among the four treatment groups, regardless of race or MetS status for the primary end point (fatal coronary heart disease or nonfatal myocardial infarction). Secondary: Significantly higher rates of heart failure were consistent across all treatment comparisons in those with MetS. Relative risks were 1.50 (95% CI, 1.18 to 1.90), 1.49 (1.17 to 1.90), and 1.88 (1.42 to 2.47) in African American participants and 1.25 (1.06 to 1.47), 1.20 (1.01 to 1.41), and 0.82 (1.51 to 2.19) in non–African American participants for amlodipine, lisinopril, and doxazosin comparisons with chlorthalidone, respectively. Higher rates for combined CVD were observed with lisinopril-chlorthalidone (RR, 1.24; 95% CI, 1.09 to 1.40; RR, 1.10; 95% CI, 1.02 to 1.19, respectively) and doxazosin-chlorthalidone comparisons (RR, 1.37; 95% CI, 1.19 to 1.58; RR, 1.18; 95% CI, 1.08 to 1.30, respectively) in African American and non–African American participants with MetS. Higher rates of stroke were seen in African American participants only (RR, 1.37; 95% CI, 1.07 to 1.76 for the lisinopril-chlorthalidone comparison, and RR, 1.49; 95% CI, 1.09 to 2.03 for the doxazosin-chlorthalidone comparison). African American patients with MetS also had higher rates of end-stage renal disease (RR, 1.70; 95% CI, 1.13 to 2.55) with lisinopril compared with chlorthalidone.
Materson et al[57]	DB, MC, RA	N=1,292	Primary: Success as defined by	Primary: Success rates were 59% for diltiazem, 51% for atenolol, 50% for clonidine,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Prazosin 4 to 20 mg QD vs HCTZ 12.5 to 50 mg QD vs atenolol 25 to 100 mg QD vs captopril 25 to 100 mg QD vs clonidine 0.2 to 0.6 mg QD vs diltiazem SR 120 to 360 mg QD vs placebo	Men with DBP of 95 to 109 mm Hg	1 year	DBP ≤95 mm Hg at one year Secondary: Not reported	46% for HCTZ, 42% for captopril, 42% for prazosin, and 25% for placebo (*P*<0.001 between diltiazem and HCTZ, atenolol and prazosin). The rates of adverse effects leading to termination of treatment were highest with prazosin at 13.8% and clonidine at 10.1%, which was significantly different from captopril at 4.8%, atenolol at 2.2%, HCTZ at 1.1%, diltiazem at 5.5%, and placebo at 6.4% (*P* values not reported). Successful blood pressure control was highest with diltiazem at 64% in African Americans, highest with captopril at 55% in younger whites, and highest with atenolol at 68% in older whites. Secondary: Not reported
Chrysant[58] Terazosin vs	DB, MC, PC, RA, Patients with inadequate control of essential hypertension	N=138 Duration not specified	Primary: Blood pressure, physical examination, electrocardiograms Secondary:	Primary: There was a significant mean reduction in supine DBP with the terazosin treated group compared with placebo (–7.3 vs -0.6 mm Hg; *P*<0.05). There were no significant changes between treatment groups in physical examinations or electrocardiograms.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo in combination with other antihypertensive agents			Not reported	Secondary: Not reported
Holtzman et al[59] Terazosin vs placebo in combination with atenolol	DB, MC, PC Patients with hypertension	N=92 10 weeks	Primary: Blood pressure, lipids profile Secondary: Not reported	Primary: There was a statistically significant reduction in supine and standing blood pressure (*P*<0.05), total cholesterol (*P*<0.05) and LDL-C plus very low density lipoprotein cholesterol levels (*P*<0.05) with the terazosin treated group. Secondary: Not reported
Os[60] Doxazosin 4 mg QD vs doxazosin 2 mg QD vs doxazosin GITS 4 mg QD	DB, PG, RA Male or female patients aged 18 to 80 diagnosed with mild-to-moderate essential hypertension (sitting DBP 95 to 110 mm Hg and SBP <180 mm Hg)	N=310 9 weeks	Primary: Efficacy, safety Secondary: Not reported	Primary: All groups had a significant decrease in blood pressure at all study visits compared with baseline. The proportion of patients who reached goal sitting DBP (<90 mm Hg) was similar among the three treatment groups, except at Week 1, when more patients in the doxazosin GITS group had obtained the goal compared with those in the doxazosin 2mg group (40.6% vs 22.3%; *P*=0.005). The proportion of patients who reached sitting SBP (<140 mm Hg) goal was similar among groups. Adverse event profiles among the groups were similar. Secondary: Not reported
Benign Prostatic Hyperplasia				
Djavan et al[61] Doxazosin vs terazosin vs	MA Men with LUTS suggestive of benign prostatic obstruction	N=6,333 (placebo-controlled trials) N=507 (comparative trials)	Primary: Total symptom score and maximum urinary flow rate, tolerability Secondary: Not reported	Primary: There was no difference in efficacy among the four drugs. Alfuzosin immediate release 2.5 mg three times daily, alfuzosin sustained-release 5 mg twice daily, terazosin 5 to 10 mg daily, doxazosin 4 to 8 mg daily, and tamsulosin 0.4 mg daily all produced comparable improvements in LUTS and maximum urinary flow rate (no *P* values reported). The total symptom score improved by 30% to 40% and the maximum urinary flow rate (Q_{max}) by 16% to 25%. Alfuzosin and tamsulosin were better tolerated than terazosin and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alfuzosin vs tamsulosin				doxazosin. Alfuzosin and tamsulosin had similar study withdrawal rates as placebo. With terazosin and doxazosin , an additional 4% to 10% of patients withdrew from the study due to intolerability (no *P* value reported). Tamsulosin had less effect on blood pressure than alfuzosin (no *P* value reported). Tamsulosin also caused less symptomatic orthostatic hypotension than terazosin (no *P* value reported). Secondary: Not reported
Samli et al[62] Doxazosin 8 mg QD vs terazosin 10 mg QD	RA, XO Men with LUTS associated with BPH	N=50 3 months	Primary: IPSS, maximum urinary flow rate Secondary: Not reported	Primary: 44% of the subjects in the doxazosin arm and 40% in the terazosin arm showed improvement in both IPSS and maximum urinary flow rate. After 3 months of treatment, both treatment groups resulted in an increased maximum urinary flow rate ($P<0.001$) and a decreased IPSS ($P<0.01$). 19 subjects did not show improvement and switched to the other treatment drug. Of these subjects, 2/19 showed improvement in both IPSS and maximum urinary flow rate, 2/19 showed improvement in IPSS only but not in maximum urinary flow rate, 15/19 did not show any improvement. Secondary: Not reported
Kaplan, Te, et al[63] Doxazosin 4 to 8 mg QD vs terazosin 5 to 10 mg QD	OL, PRO Men with BPH and >80 years of age	N=36 6 months	Primary: Peak urinary flow rate, AUA SS Secondary: Not reported	Primary: There was significant improvement in maximum urinary flow rate ($P<0.008$) and AUA SS ($P<0.01$) in both treatment groups. There were small, non-significant decreases in blood pressure. Secondary: Not reported
Kaplan, Soldo, et al[64] Doxazosin 4 mg QAM (DOX-AM)	PI, RA Normotensive men with symptomatic prostatism	N=43 4 to 17 months	Primary: Boyarsky symptom score, peak urinary flow rate, blood pressure, and occurrence of	Primary: There were significant improvements from baseline in Boyarsky symptom score and maximum urinary flow rate in all four treatment groups ($P<0.05$). There was no significant difference in Boyarsky symptom score and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs doxazosin 4 mg QPM (DOX-PM) vs terazosin 5 mg QAM (TER-AM) vs terazosin 5 mg QPM (TER-PM)			adverse events Secondary: Not reported	maximum urinary flow rate improvement between the four groups. Adverse events were significantly decreased in groups with evening administration dosing schedule (*P*<0.05). Secondary: Not reported
Bozlu et al[65] Doxazosin 4 mg QD vs terazosin 5 mg QD vs alfuzosin 2.5 mg TID vs tamsulosin 0.4 mg QD	RETRO Patients with LUTS suggestive of BPH with and without diabetes	N=281 6 months	Primary: Symptoms and bother score according to the Turkish validation of the IPSS, maximum flow rate, post-void residual urine volume Secondary: Not reported	Primary: α1-Blockers significantly improved the IPSS, bother score, maximum urinary flow rate, and post-void residual urine volume compared with baseline (*P*<0.001). IPSS and bother score were significantly improved more in the diabetic patients compared with the nondiabetic patients (*P*<0.01). There was no significant difference among the groups in the improvement rates of any of the parameters (*P*>0.05). Secondary: Not reported
Xue et al[66] Doxazosin (controlled-release) 4 mg QD vs tamsulosin 0.2 mg QD	RCT Chinese men with confirmed BPH	N=117 8 weeks	Primary: Efficacy, safety Secondary: Not reported	Primary: Both drugs significantly improved the IPSS (total, irritative subscore, and obstructive subscore. *P*=0.001 for all) and maximum urinary flow rate (*P*=0.001). Other differences between groups were not statistically significant. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rahardjo et al[67] Doxazosin 2 mg QD vs tamsulosin 0.2 mg QD	MC, OL, RA Patients with LUTS due to BPH	N=101 6 weeks	Primary: IPSS, maximal urinary flow rate, average urinary flow rate and residual urine; safety Secondary: Not reported	Primary: The total IPSS decreased significantly in both the tamsulosin and doxazosin groups compared to baseline (*P*<0.001). There was a significant difference in the decrease in total IPSS between two groups (*P*=0.036). Maximal urinary flow rate, average urinary flow rate and residual urine significantly improved only in the tamsulosin group (*P*<0.001, *P*<0.001, and *P*<0.05, respectively). There were no significant differences in SBP, DBP or heart rate profile in the tamsulosin group; however, doxazosin resulted in a significant difference from baseline in SBP (*P*<0.01) but not in DBP (*P*=NS) at the end of the study. Tamsulosin was well tolerated; only three patients (6%) in the tamsulosin group reported an adverse event (dizziness) while 11 patients (22%) in the doxazosin group reported an adverse event (dizziness), one of whom withdrew from the study. Secondary: Not reported
Pompeo et al[68] Doxazosin GITS 4 mg plus tamsulosin placebo QID vs tamsulosin 0.4 mg plus doxazosin placebo QID	DB, DD, RA Brazilian patients with BPH	N=165 12 week	Primary: Absolute and percentage change from baseline in symptoms measured by IPSS Secondary: QOL question from the IPSS, questions 6 and 7 of the SFAQ	Primary: Doxazosin GITS and tamsulosin improved IPSS with no significant differences between groups at week 12. During weeks 4 to 8, tamsulosin-treated patients demonstrated a slower improvement (*P*<0.001) in IPSS than doxazosin GITS-treated patients. Secondary: The proportion of satisfied patients did not change over the course of the study with doxazosin GITS, while it did change significantly between weeks 4 and 8 with tamsulosin (*P*=0.006); this suggests that a change for the better was observed earlier with doxazosin. At week 12, the proportion of patients with little or no difficulty at ejaculation (question 6 of SFAQ) was higher in the doxazosin GITS group (*P*=0.019). Both treatments were well tolerated.
Johnson et al[69]	PC, RA	N=3,047	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Doxazosin (2, 4, 8 mg) QD vs finasteride 5 mg QD vs doxazosin (2, 4, 8 mg) QD and finasteride 5 mg QD vs placebo	Men with LUTS suggestive of BPH	4 years	Efficacy (mean reduction in self-reported nightly nocturia at 1 and 4 years) Secondary: Not reported	The number of men reporting 1 or more episodes of nocturia who finished 12 or more months of the trial came to a total of 2,583. Mean nocturia was similar in all groups at baseline. Mean nocturia was reduced at 1 year by 0.35, 0.40, 0.54 and 0.58 in the placebo, finasteride, doxazosin and combination groups, respectively. Reductions with doxazosin and combination therapy were statistically greater than with placebo ($P<0.05$). At 4 years, nocturia was also significantly reduced in patients treated with doxazosin and combination therapy ($P<0.05$ vs placebo). In men older than 70 years (n=495) all drugs significantly reduced nocturia at 1 year (finasteride 0.29, doxazosin 0.46 and combination 0.42) compared to placebo (0.11; $P<0.05$). Secondary: Not reported
Crawford et al[70] Doxazosin 4 to 8 mg QD vs finasteride 5 mg QD vs doxazosin 4 to 8 mg QD and finasteride 5 mg QD vs placebo	PC, RA Men with LUTS suggestive of BPH	N=737 4 years	Primary: Time to overall clinical progression of BPH, defined as either a confirmed 4-point or greater increase in AUA SS, acute urinary retention, incontinence, renal insufficiency, or recurrent urinary tract infection Secondary: Not reported	Primary: The rate of overall clinical progression of BPH events in the placebo group was 4.5 per 100 person-years, for a cumulative incidence (among men who had at least 4 years of followup data) of 17%. The risk of BPH progression was significantly greater in patients on placebo with a baseline TPV of ≥31 mL vs those with a baseline TPV <31 mL ($P<0.0001$). The risk of BPH progression was significantly greater in patients on placebo with a baseline PSA of ≥1.6 ng/dL vs those with a baseline PSA <1.6 ng/dL ($P=0.0009$). The risk of BPH progression was significantly greater in patients on placebo with, a baseline maximal urinary flow rate of less than 10.6 mL per second vs those with a baseline maximal urinary flow rate ≥10.6 mL per second ($P=0.011$) The risk of BPH progression was significantly greater in patients on placebo with a baseline PVR of ≥39 mL vs those with a baseline PVR less

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				than 39 mL (*P*=0.0008). The risk of BPH progression was significantly greater in patients on placebo with baseline age ≥62 years or older vs those aged <62 years (*P*=0.0002). Secondary: Not reported
Kaplan, McConnell, et al[71] Doxazosin 4 to 8 mg QD vs finasteride 5 mg QD vs doxazosin 4 to 8 mg QD and finasteride 5 mg QD vs placebo	PC, RA Men with LUTS suggestive of BPH	N=3,047 4 years	Primary: Overall clinical progression of BPH (defined as a confirmed 4 point or greater increase in AUA SS, acute urinary retention, incontinence, renal insufficiency or recurrent urinary tract infection) Secondary: Need for invasive therapy for BPH, AUA SS, maximum urinary flow rate with time	Primary: In patients with a small prostate (baseline TPV >25 mL) combination therapy was no better than doxazosin alone for decreasing the risk of clinical progression of BPH and need for invasive therapy as well as improving AUA SS and the maximum urinary flow rate. However, in patients with moderate size (25 to >40 mL) or enlarged (≥40 mL) glands, combination therapy led to a clinical benefit in these outcomes that was superior to that of doxazosin or finasteride (*P*<0.05). Secondary: In men with baseline TPV <25 mL, there was no significant difference in the risk of invasive therapy for combination therapy relative to doxazosin or finasteride alone. However, in the baseline TPV subgroups of 25 to <40 mL and ≥40 mL there was a significant and marked percent risk decrease in invasive therapy, of around 60% to 80% for combination therapy vs doxazosin alone (*P*<0.05). In men with baseline TPV <25 mL the improvement at year 4 in AUA SS for combination therapy relative to doxazosin alone was not significantly different, whereas the improvement for combination therapy vs finasteride alone was significantly different in favor of combination therapy (*P*<0.05). In the baseline TPV subgroups of 25 to <40 mL and ≥40 mL, the improvement in AUA SS with combination therapy was significantly better than that for doxazosin alone and finasteride alone (*P*<0.05).
Tsujii[72] Prazosin 0.5 to 1 mg BID	RA, XO Patients with symptomatic BPH	N=121 4 weeks	Primary: Symptom score, changes in maximum and average urinary	Primary: The terazosin-treated group showed significant improvement in 4 out of 9 symptoms compared with tamsulosin (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs terazosin 0.5 to 1 mg BID vs tamsulosin 0.1 to 0.2 QD			flow rate , postvoid residual urine volume, and blood pressure Secondary: Not reported	There were significant increases in maximum urinary flow rate with the prazosin group, and in average urinary flow rate with the tamsulosin groups (*P*<0.05). There were no significant changes in residual urine volume with any of the treatment groups. Significant blood pressure reductions were observed in the hypertensive subjects in the prazosin, terazosin, and tamsulosin groups (*P*<0.05 for all). In the normotensive subjects, no significant changes in blood pressure were observed with any of the drugs. Secondary: Not reported
Tsai et al[73] Group A: Terazosin (generic) 1 - 4 mg QD during period 1 and terazosin (brand ®) 1 - 4 mg QD in period 2 (6 weeks) vs Group B: Terazosin (brand) 1 - 4 mg QD during period 1 and terazosin (generic) 1 - 4 mg QD in period 2 (6 weeks) The generic terazosin employed was manufactured by Purzer Pharmaceutical Co, Taipei, Taiwan.	CO, OL, RA Adult men in Taiwan newly diagnosed with symptomatic BPH who had not previously received treatment for BPH	N=53 13 weeks	Primary: IPSS, tolerability (using physical examination, including vital signs; laboratory analysis; and spontaneous reporting) Secondary: Not reported	Primary: At 2 and 6 weeks, no significant between-product differences were found in mean (SD) decreases from baseline in IPSS total score (generic, 2.46 [0.84] and 2.46 [1.00], respectively; branded, 1.56 [0.60] and 2.87 [0.71]) (*P*=0.29). At week 6, the between-product difference in mean (SD) increase from baseline in maximal uroflow rate was non-significant (generic, 2.36 [0.90] mL/s; branded, 2.03 [0.62] mL/s) (*P*=0.72). A total of 86 treatment-emergent adverse events were reported (45 with the generic drug; 41 with the branded drug), all of which were considered by the investigator as non-serious except for 1 case of acute epididymitis, which occurred with the generic drug. The most common adverse events reported with the generic and branded formulations were dizziness (7/48 [14.6%] and 10/50 [20.0%], respectively) and peripheral edema (1/48 [2.1%] and 3/50 [6.0%]). No significant differences in the prevalence of adverse events were found between the 2 treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Yang et al[74] Terazosin 2 mg QD for 1 week Those patients with continued LUTS after the initial treatment were allocated randomly into two groups: terazosin 2 mg QD for six weeks vs terazosin 2 mg QD and tolterodine 2 mg BID for six weeks	COMBO Patients diagnosed with LUTS due to BPH	N=69 7 weeks	Primary: IPSS Secondary: Not reported	Primary: The IPSS were significantly improved in both groups after treatment, and the reduction of IPSS in the combination group was significantly greater than that in the terazosin group (P<0.01). A decrease in urgency, frequency and nocturia were the main contributory factors causing the reduction of IPSS in the combination group. The differences about the peak urinary flow rate and the residual urine from the baseline values were noted in both groups after treatment, but were not significant between the two groups. The incidence of adverse effects in the combination group was higher than that in the terazosin group. As expected, the most common adverse effect was mouth dryness, which is associated with anticholinergic drugs such as tolterodine. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QAM=once in the morning, QD=once daily, QID=four times a day, QPM=once in the evening, SR=sustained-release, TID=three times a day
Study abbreviations: AC=active-controlled, CI=confidence interval, COMP=comparative, CON=controlled, DB=double-blind, DD=double-dummy, LSR= Latin-square randomization , MA= Meta-analysis, MC=multi-center, NC=non-comparative, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, PI=pilot study, PRO=prospective, RA=randomized, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SD=standard deviation, TW=three-way, XO=crossover
Miscellaneous abbreviations: AUA SS=American Urological Association symptom score, β-blockers=β-adrenergic blocking agents, BPH=Benign Prostatic Hyperplasia, bpm=beats per minute, CVD=cardiovascular disease, DBP=diastolic blood pressure, GITS=gastrointestinal therapeutic system, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, IPSS=International Prostatic Symptom Score, LDL-C =low-density lipoprotein cholesterol, LUTS=lower urinary tract symptoms, MetS=cardiometabolic syndrome, PSA=Prostate specific antigen, PVR=post-void residual urine volume, Qmax=maximum urinary flow rate, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, SFAQ=Sexual Function Abbreviated Questionnaire, TPV=total prostate volume

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on physician visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 α-Adrenergic Blocking Agents

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
doxazosin	sustained-release tablet, tablet	Cardura®*, Cardura XL®	$$	$
prazosin	capsule	Minipress®*	$	$
terazosin	capsule	Hytrin®*	$$$	$

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

X. Conclusions

α-Adrenergic blocking agents (α_1-blockers) have been shown to be significantly more efficacious than placebo in reducing blood pressure. In clinical trials, α_1-blockers were as effective as other classes of antihypertensive agents (angiotensin-converting enzyme inhibitors, calcium channel blocking agents and β-adrenergic blocking agents (β-blockers) in lowering blood pressure when titrated over the usual dosage ranges. There were no significant differences in diastolic blood pressure reductions between the drug treatments. Trials in which α_1-blockers were added as part of a combination regimen for treatment of resistant hypertension resulted in further reductions in blood pressure.

However, blood pressure reduction is only a surrogate marker. The ultimate goal of antihypertensive therapy is to reduce cardiovascular morbidity and mortality. Earlier studies have used the Framingham formula to calculate the coronary heart disease (CHD) risk by taking into account systolic blood pressure, total cholesterol, high-density

lipoprotein cholesterol, presence of left ventricular hypertrophy, presence of glucose intolerance, and use of cigarettes. Using the Framingham formula, treatment with doxazosin resulted in a decrease in CHD risk by 15% to 45% compared with baseline.[75]

ALLHAT is the only large trial to date that studied the effects on cardiovascular morbidity and mortality of α_1-blockers compared with the other classes of antihypertensive drugs.[10] In this trial, an α_1-blocker, doxazosin, was observed to increase the risks of stroke and combined cardiovascular events, although it provided certain other benefits including improvements in insulin resistance and lipid abnormalities. Therefore, α_1-blockers are no longer regarded as first-line therapy for the treatment of hypertension according to many national and international guidelines.[8,13-20] α_1-Blockers may be therapeutic options in multidrug regimens for the treatment of resistant hypertension.

It has been suggested that α_1-blockers be used for the treatment of benign prostatic hyperplasia (BPH) only in patients without hypertension or in patients with stages 1 or 2 hypertension who are at low risk for congestive heart failure.[76] Caution should be used when α_1-blockers are used, even as add-on therapy in hypertension or for symptomatic relief of BPH in patients at risk for congestive heart failure.[77]

There is no evidence that shows any one of the α-adrenergic blocking agents included in this review to be more efficacious than the others for the treatment of hypertension or BPH. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class, and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand α-adrenergic blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 β-Adrenergic Blocking Agents
Single Entity Agents
AHFS Class 242400
September 10, 2008

I. Overview

The β-adrenergic blocking agents (β-blockers) are a class of medications that can be further categorized by their pharmacologic and pharmacokinetic properties. The β-blockers differ in their adrenergic-receptor blocking, membrane stabilizing, and intrinsic sympathomimetic activities and lipophilicity.[1-3] The differences in these pharmacologic properties lead to differences in indications and side effects. Most of the β-blockers are approved for the treatment of hypertension. Other indications include angina pectoris, cardiac arrhythmias, heart failure, migraine prophylaxis and myocardial infarction. "Despite the extensive experience with β-blockers in clinical practice, there have been no studies suggesting that any of these agents have major advantages or disadvantages in relation to the others for the treatment of many cardiovascular diseases. When any available β-blocker is titrated properly, it can be effective in patients with an arrhythmia, hypertension, or angina pectoris."[2]

The single entity β-blockers that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Single Entity β-Adrenergic Blocking Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
acebutolol	capsule	Sectral®*	acebutolol
atenolol	injection, tablet	Tenormin®*	atenolol
betaxolol	tablet	Kerlone®*	betaxolol
bisoprolol	tablet	Zebeta®*	bisoprolol
carvedilol	extended-release capsule, tablet	Coreg®*, Coreg CR®	Coreg®*, Coreg CR®, carvedilol
esmolol^	injection	Brevibloc®*	none
labetalol	injection, tablet	Normodyne®*†, Trandate®*	labetalol
metoprolol succinate	extended-release tablet	Toprol XL®*	metoprolol succinate
metoprolol tartrate	injection, tablet	Lopressor®*	metoprolol tartrate
nadolol	tablet	Corgard®*	nadolol
nebivolol	tablet	Bystolic®	none
penbutolol	tablet	Levatol®	none
pindolol	tablet	Visken®*†	pindolol
propranolol	injection, solution, extended-release capsule, long-acting capsule, tablet	Inderal®*, Inderal LA®*, InnoPran XL®*	propranolol
sotalol	tablet	Betapace®*, Betapace AF®*	sotalol
timolol	tablet	Blocadren®*†	timolol

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
^Product is primarily administered in an institution.

There are at least three distinct types of β receptors distributed throughout the body, β_1, β_2, and β_3 receptors. β_1 receptors are located predominantly in the heart and kidney. Agents that have a greater affinity to β_1 receptors are considered to be cardioselective. The cardioselectivity of the β-blockers is highlighted in Table 2. Cardioselective agents may be safer in patients with asthma, chronic obstructive pulmonary disease and peripheral vascular disease

because they produce less inhibition of the β_2 receptors, which mediate vasoconstriction and bronchospasm. Cardioselectivity is dose dependent; therefore, β_2 blockade can occur at higher doses with these agents.[1]

Table 2. Selected Pharmacologic Properties of the Single Entity β-Adrenergic Blocking Agents[1-42]

Drug	Adrenergic-Receptor Blocking Activity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity
Acebutolol	β_1*	+†	+
Atenolol	β_1*	0	0
Betaxolol	β_1*	+	0
Bisoprolol	β_1*	0	0
Carvedilol	α_1 - β_1 - β_2	++	0
Esmolol	β_1*	0	0
Labetalol	α_1 - β_1 - β_2	0	+
Metoprolol	β_1*	0†	0
Nadolol	β_1 - β_2	0	0
Nebivolol	β_1*	0	0
Penbutolol	β_1 - β_2	0	+
Pindolol	β_1 - β_2	+	++
Propranolol	β_1 - β_2	++	0
Sotalol	β_1 - β_2	0	0
Timolol	β_1 - β_2	0	0

0=none; +=low; ++=moderate; +++ high
*Inhibits β_2 receptors (bronchial and vascular) at higher doses.
†Detectable only at doses much greater than required for β blockade.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines using single entity β-adrenergic blocking agents (β-blockers) are listed in Table 3. For a comprehensive overview of the pharmacologic management of acute myocardial infarction, angina pectoris, chronic heart failure, and hypertension, please refer to the Appendix.

Table 3. Treatment Guidelines Using the Single Entity β-Adrenergic Blocking Agents

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)[43]**	<u>Initial and Hospital Management</u> • Oxygen, morphine, nitroglycerin (NTG), angiotensin-converting enzyme inhibitors (ACE inhibitors), β-blockers, and aspirin may be used in patients presenting with a myocardial infarction (MI). Patients should be considered for reperfusion therapy. • All patients should continue receiving β-blockers unless contraindicated. • Patients that did not receive β-blockers within 24 hours of ST-Elevation Myocardial Infarction (STEMI) should be started on these agents unless contraindicated. • Patients with early contraindications to β-blockers should be reevaluated for candidacy for β-blocker therapy. • Patients with moderate or severe left ventricular failure should receive β-blockers as secondary prevention and the dose should be titrated slowly. <u>Secondary Prevention</u> • Patients with co morbid hypertension should be treated initially with β-blockers and/or ACE inhibitors with the addition of other medication as needed to achieve a blood pressure goal of <140/90 mm Hg (or <130/80 mm Hg in patients with diabetes or chronic kidney disease). • β-Blockers should be initiated and continued in all patients who have had an MI, acute coronary syndrome (ACS), or left ventricular dysfunction with or without heart failure symptoms (unless contraindicated).
National Institute for Health and Clinical Excellence (NICE):	• The following medications are recommended for all patients who have had an MI: an ACE inhibitor, aspirin, β-blockers, and a hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin).

Clinical Guideline	Recommendation
Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)[44]	• All patients should be offered treatment with a β-blocker after an MI. Patients with left ventricular systolic dysfunction and/or heart failure should be managed according to recommendations for chronic heart failure. Clinicians may want to consider use of a β-blocker which is licensed for use in heart failure. • After a proven MI in the past, asymptomatic patients with preserved left ventricular function should not routinely be offered a β-blocker unless they are at risk for further cardiovascular events or other compelling indications exist. • Verapamil or diltiazem may be considered for secondary prevention in patients without pulmonary congestion or left ventricular systolic dysfunction in whom β-blockers must be discontinued or in whom β-blockers are contraindicated.
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)**[45]	Prophylactic Therapies in the Acute Phase • Oral β-blockers should suffice in most cases. An intravenous (IV) β-blocker may be used especially in tachycardia (in absence of heart failure), relative hypertension and pain unresponsive to opiates unless contraindicated. Secondary Prevention • β-blockers are recommended for all patients unless contraindicated. • Diltiazem or verapamil may be appropriate if β-blockers are contraindicated in the absence of heart failure.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[43]	• Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including ACE inhibitors and/or β-blockers with the addition of other medications as needed to achieve blood pressure goals of <140/90 mm Hg or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Aldosterone blockers are recommended in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a left ventricular ejection fraction ≤40% and have either diabetes or heart failure. • β-Blocker therapy is recommended indefinitely in all patients who have had an MI, ACS, or left ventricular dysfunction with or without heart failure symptoms unless contraindicated. • Long-acting calcium-channel blocking agents (CCBs) or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine CCBs can increase adverse cardiac events and should not be used. • Long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful.
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[44]	• Nitrates, morphine, β-blockers, CCBs, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet agents, and GP IIb/IIIa receptor antagonists can be used in the acute setting during early hospitalization. • β-Blockers are recommended in all patients unless otherwise contraindicated. Treatment should be initiated acutely or within a few days of the event and continued indefinitely. In patients with moderate-to-severe left ventricular failure, β-blockers should be titrated gradually. • CCBs are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. • For patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with chronic kidney disease or diabetes), it is useful to add blood pressure medication(s) as tolerated, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs such as thiazide diuretics as needed to achieve target blood pressure. • Nitrates, β-blockers, and CCBs (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)**[45]	Therapy to Improve Prognosis • β-blockers are recommended as first-line therapy in patients with angina in the absence of contraindications. • CCBs may be recommended in patients with angina who cannot tolerate β-blockers and who

Clinical Guideline	Recommendation
	have had an MI and who do not have heart failure. Symptomatic Treatment and Treatment of Ischemia • β-blockers should be titrated to full dose. Considerations should be given for 24-hour prophylaxis against ischemia. • If patients are intolerant to β-blocker therapy, consideration may be given to a CCB or a long-acting nitrate. Sinus node inhibition may be considered. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. If combination β-blocker and CCB therapy is insufficient, a long-acting nitrate may be substituted for the CCB. Treatment of Syndrome X • Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS) (2007)**[46]	• β-blockers are recommended in most patients (in the absence of contraindications), especially in patients with hypertension or tachycardia. • CCBs may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina. • Nondihydropyridine CCBs should not be used unless combined with β-blockers. • β-blockers should be initiated in all patients with left ventricular dysfunction. • Aldosterone antagonists should be considered in patients who are already on an ACE inhibitor and β-blocker after an MI, who have a left ventricular ejection fraction of ≤40%, diabetes, or heart failure and who do not have significant renal dysfunction or hyperkalemia.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease (2004)**[47]	Symptomatic Patients • The following agents are recommended to prevent MI or death and to reduce symptoms: aspirin (clopidogrel may be used in patients intolerant to aspirin), β-blockers, statins, and ACE inhibitors. • The following agents are recommended to reduce symptoms only: NTG (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when monotherapy has been unsuccessful. Asymptomatic Patients With Evidence Suggesting CAD on Previous Testing • The following agents should be used to prevent MI and death: aspirin (in patients with a previous MI), β-blockers (in patients with a previous MI), statins (in patients with type 2 diabetes or documented CAD), and an ACE inhibitor (in patients with documented CAD and diabetes, systolic dysfunction, or both).
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[48]	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors, and β-blockers have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Cardiac Structural Abnormalities or Remodeling Who Have not Developed Heart Failure Symptoms (Stage B) • β-Blockers and ACE inhibitors should be used in all patients with a recent or past history of MI. • β-Blockers and ACE inhibitors should be used in patients who have reduced left ventricular ejection fraction and do not have a history of MI or heart failure. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • β-Blockers (bisoprolol, carvedilol, or extended-release metoprolol) are recommended in all stable patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated.

Clinical Guideline	Recommendation
	• The addition of a nitrate and hydralazine is reasonable in patients with reduced left ventricular ejection fraction already on an ACE inhibitor and β-blocker and who have persistent symptoms. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • β-Blockers, ARBs, ACE inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms. Special Populations • Hydralazine and isosorbide dinitrate may be beneficial when added to the standard treatment including β-blockers and ACE inhibitors in African American patients with New York Heart Association (NYHA) functional class III or IV. Patients with Concomitant Disorders • Nitrates and β-blockers are recommended in patients with heart failure and angina. • In patients with atrial fibrillation, ventricular response rate should be controlled with a β-blocker or amiodarone (if a β-blocker is not tolerated).
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[49]	• β-Blockers are recommended in patients who have had an MI to reduce mortality, recurrent MI, and prevent heart failure. Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction • β-Blocker therapy is recommended. Patients With Left Ventricular Systolic Dysfunction • β-Blockers should be used in all patients with a left ventricular ejection fraction ≤40%, unless otherwise contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a left ventricular ejection fraction ≤40%. • β-Blocker therapy is recommended in patients with recent decompensation of heart failure after stabilization and discontinuation of IV vasoactive agents and diuretics. • β-Blockers are recommended regardless of the presence of diabetes, chronic obstructive lung disease, or peripheral vascular disease, though caution is recommended in patients with diabetes with recurrent hypoglycemia, asthma, or resting limb ischemia. Considerable caution is recommended in patients with marked bradycardia (<55 beats per minute) or hypotension (systolic blood pressure <80 mm Hg). • β-Blockers are not recommended in patients with asthma with active bronchospasm. • It is recommended that the dose of β-blocker therapy be titrated slowly. Therapy should continue in most cases during symptomatic exacerbations, though the dose may need to be decreased. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had an MI and have left ventricular dysfunction is not recommended. • An aldosterone antagonist should be considered in patients who have had an MI and who have symptomatic heart failure and left ventricular ejection fraction ≤40% while receiving standard therapy with an ACE inhibitor (or ARB) and a β-blocker. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • β-blockers are recommended in patients with heart failure and preserved left ventricular ejection fraction who have also had an MI, hypertension, or atrial fibrillation requiring ventricular rate control. • CCBs should be considered in patients who have hypertension (amlodipine should be considered) or angina, and in those who have atrial fibrillation requiring ventricular rate control and are intolerant to β-blockers. Patients With Heart Failure and Coronary Artery Disease

Clinical Guideline	Recommendation
	• β-blockers are recommended in patients with reduced left ventricular ejection fraction and in patients who have had an MI. • ACE inhibitor and β-blocker therapy should be initiated early (within <48 hours) in hospitalized stable patients who have had an MI and have left ventricular dysfunction. • CCBs should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Managing Patients With Heart Failure and Hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or CCB. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent. • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing CCB (amlodipine) may be considered. <u>Managing Heart Failure in the Elderly, Women, and African Americans</u> • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. • Hydralazine and isosorbide dinitrate are recommended in all African American patients (in addition to standard therapy with ACE inhibitors and β-blockers) with left ventricular systolic dysfunction who are in NYHA classes II-IV.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)**[50]	• Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated. • β-blockers are recommended in all patients with heart failure. Carvedilol, metoprolol succinate, and bisoprolol are the recommended β-blocking agents. Small initial doses are recommended, titrating upward as tolerated. • Aldosterone antagonists are recommended in addition to ACE inhibitors, β-blockers, and diuretics in patients who have advanced heart failure (NYHA class III-IV) with systolic dysfunction, and in patients who are unable to tolerate therapy with ACE inhibitors. • Aldosterone antagonists are recommended in combination with an ACE inhibitor and a β-blocker in patients who have had an MI and who have left ventricular systolic dysfunction and signs of heart failure. • A combination of digoxin and a β-blocker seems to be more efficacious to either agent alone in patients with atrial fibrillation. Digoxin may reduce hospitalizations in patients with heart failure caused by left ventricular systolic dysfunction and sinus rhythm who are already treated with ACE inhibitors, β-blockers, diuretics, and spironolactone (in severe heart failure). • The CCBs diltiazem and verapamil are not recommended in patients with heart failure caused by systolic dysfunction. The addition of felodipine or amlodipine does not improve survival or symptoms, though may be helpful in patients with angina or arterial hypertension not controlled with nitrates and β-blockers. • Antiarrhythmic therapy may be indicated in patients with heart failure and atrial fibrillation

Clinical Guideline	Recommendation
	or ventricular tachycardia. Class I antiarrhythmics should be avoided. β-blockers may be used alone or in combination with amiodarone in patients with ventricular tachyarrhythmias. Amiodarone may be used in patients with ventricular and supraventricular tachyarrhythmias. It is preferred in patients with heart failure and atrial fibrillation and may improve the success of electrical cardioversion. Routine administration of amiodarone is not recommended.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[51]	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • In patients with ACS (MI or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. Other medications may be used as needed for blood pressure control. • For patients with post-MI, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients. • Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators. • β-Blockers are useful in the treatment and/or prophylaxis of atrial arrhythmias/fibrillation, migraine, thyrotoxicosis (short term), essential tremor, and perioperative hypertension. • β-Blockers should be used cautiously or avoided in patients with asthma, reactive airways disease, or second or third degree heart block.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[52]	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[53]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, non dihydropyridine CCBs), end stage renal

Clinical Guideline	Recommendation
	disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[54]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[55]	• If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • β-blockers are generally not preferred for initial therapy for hypertension, though they may be used in younger patients in the case of ACE inhibitor and ARB intolerance, in women of childbearing age, and in patients with an increased sympathetic drive. • If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes). • Patients who are well-controlled on a β-blocker do not need to be switched from the β-blocker to an alternative agent. • If a β-blocker is to be discontinued, the dose should be gradually decreased. β-blockers should not be discontinued in patients who have a compelling indication for β-blockade, including those with angina and those who have had an MI.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[56]	• No specific recommendation is made concerning single entity β-blockers.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[57]	• No specific recommendation is made concerning single entity β-blockers.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[58]	• ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney**	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed

Clinical Guideline	Recommendation
Disease (2004)[59]	by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.
American College of Cardiology (ACC)/ American Heart Association (AHA)/European Society of Cardiology (ESC) Committee for Practice Guidelines: **Guidelines for the Management of Patients With Atrial Fibrillation (2006)**[63]	Pharmacological Rate Control During Atrial Fibrillation • For patients with persistent and permanent atrial fibrillation (AF), a β-blocker or a nondihydropyridine calcium channel antagonist is recommended for rate control. • In an acute setting and in the absence of preexcitation, IV β-blockers or a nondihydropyridine calcium channel antagonist are recommended for slow rate. • To control heart rate at rest or during exercise, digoxin in combination with a β-blocker or a nondihydropyridine calcium channel antagonist are reasonable treatment options. Cardioversion of Atrial Fibrillation • Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF. • Before antiarrhythmic medication is initiated, a beta blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs. • Sotalol and digoxin may be harmful when used for pharmacological cardioversion of AF and are not recommended. • Sotalol, amiodarone, flecainide, ibutilide or propafenone can be useful to enhance the success of direct-current cardioversion and prevent recurrent AF. • For patients with persistent AF, administration of β-blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of AF is uncertain. Maintenance of Sinus Rhythm • Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. • Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms, serum electrolytes are normal, and risk factors associated with class III drug-related proarrhythmia are not present. Special Considerations • For patients undergoing cardiac surgery, it is recommended to treat these patients with a β-blocker to prevent postoperative AF. • Prophylactic administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery. • In patients with an acute MI with AF who lack left ventricular dysfunction, bronchospasm, or AV block, an IV β-blocker or a nondihydropyridine calcium antagonist is recommended to slow the rapid ventricular response. • To control the ventricular response rate in patients with AF and concomitant thyrotoxicosis, a β-blocker is recommended. • In pregnant patients with AF, a β-blocker, digoxin or a nondihydropyridine calcium channel antagonist is recommended to control the rate of ventricular response. • In patients with hypertrophic cardiomyopathy, antiarrhythmic medications can be useful to prevent recurrent. Although there is a lack of data for this indication, disopyramide combined with a β-blocker or nondihydropyridine calcium channel antagonist or amiodarone alone is generally preferred.

Clinical Guideline	Recommendation
	• In those patients with AF and concurrent obstructive lung disease, therapy with a nondihydropyridine calcium channel antagonist is recommended to control ventricular rate. Therapy with β-blockers, sotalol, propafenone, and adenosine are not recommended.
American College of Cardiology (ACC) /American Heart Association (AHA)/European Society of Cardiology (ESC) Committee for Practice Guidelines: **Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2006)**[64]	Drug therapy for Ventricular Arrhythmias • β-Blockers are currently the mainstay of pharmacologic therapy for the treatment of arrhythmias, due to their safety profile and effectiveness. • Other than β-blockers, alternative antiarrhythmic agents currently available have not have not been proven effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of sudden cardiac death (SCD). • β-blockers, or alternatively, amiodarone or sotalol, may be used in patients with ventricular tachycardia (VT) who do not meet criteria for an implantable cardioverter-defibrillator (ICD). • Sotalol or, alternatively the combination of β-blockers and amiodarone, may be used in patients with ICDs who have recurrent VT/ ventricular fibrillation (VF) with frequent appropriate ICD firing. Ventricular Arrhythmia and Sudden Cardiac Death Related to Specific Pathology Left Ventricular (LV) Dysfunction Due to Prior MI: • Amiodarone, often in combination with β-blockers, can be useful for patients with LV dysfunction due to prior MI and symptoms due to VT unresponsive to β-blocking agents. • Sotalol is reasonable therapy to reduce symptoms resulting from VT for patients with LV dysfunction due to prior MI unresponsive to β-blocking agents. • Alternative therapies to the ICD to improve symptoms due to frequent episodes of sustained VT or VF in patients with LV dysfunction due to prior MI include agents such as amiodarone or sotalol. • Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. Congenital Heart Disease: • Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with congenital heart disease and isolated premature ventricular contractions (PVCs). Metabolic and Inflammatory Conditions: • Antiarrhythmic therapy can be useful in patients with symptomatic nonsustained VT or sustained VT during the acute phase of myocarditis. Pericardial Disease: • Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of SCD in patients with pulmonary arterial hypertension or other pulmonary conditions. Ventricular Arrhythmias Associated With Cardiomyopathies Arrhythmogenic Right Ventricular (RV) Cardiomyopathy: • Amiodarone or sotalol can be effective for treatment of sustained VT or VF in patients with arrhythmogenic RV cardiomyopathy when ICD implantation is not feasible. Heart Failure • Amiodarone, sotalol and/or other β-blockers are recommended pharmacological adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with HF. • Amiodarone, sotalol, and/or β-blockers may be considered as pharmacological alternatives to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with HF for whom ICD therapy is not feasible.

Clinical Guideline	Recommendation
	Genetic Arrhythmia Syndromes Long QT Syndrome (LQTS): • β-Blockers are recommended for patients with an LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval). • Implantation of an ICD along with use of β-blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. • β-Blockers can be effective to reduce SCD in patients with a molecular LQTS analysis and normal QT interval. • Implantation of an ICD with continued use of β-blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT while receiving β-blockers and who have reasonable expectation of survival with a good functional status for more than 1 year. Catecholaminergic Polymorphic Ventricular Tachycardia: • β-Blockers are indicated for patients who are clinically diagnosed with catecholaminergic polymorphic VT on the basis of the presence of spontaneous or documented stress-induced ventricular arrhythmias. • β-Blockers can be effective in patients without clinical manifestations when the diagnosis of catecholaminergic polymorphic VT is established during childhood based on genetic analysis. • β-Blockers may be considered for patients with catecholaminergic polymorphic VT who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. Arrhythmias in Structurally Normal Hearts Idiopathic Ventricular Tachycardia: • Drug therapy with β-blockers and/or calcium channel blockers can be useful in patients with structurally normal hearts with symptomatic VT arising from the right ventricle. Ventricular Arrhythmias and Sudden Cardiac Death Related to Specific Populations • In pregnant women with the LQTS who have had symptoms, it is beneficial to continue β-blocker medications throughout pregnancy and afterward, unless there are definite contraindications. • The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients.
National Cancer Institute (NCI): **Pheochromocytoma Treatment, Physician Data Query (PDQ®) (2008)**[65]	• Initial treatment of pheochromocytoma following diagnosis focuses on blocking of alpha-adrenergic activity with the administration of phenoxybenzamine or an α_1-adrenergic receptor antagonist, such as prazosin. • Once alpha blockade is established, β-blockers may be used to control symptoms manifestations caused by pheochromocytoma, such as hypertension and tachyarrhythmias. • If the pheochromocytoma tumor cannot be removed, a combination of α-blockers and β-blockers may be used long-term to control symptoms.
American Academy of Family Physicians (AAFP)/American College of Physicians-American Society of Internal Medicine (ACP-ASIM): **Guideline on the Management and Prevention of Migraines**[66]	• Use nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy and migraine-specific agents (i.e., oral naratriptan or rizatriptan, SC or oral sumatriptan, and oral zolmitriptan) in patients who have failed NSAID therapy. • Preventative medications should be considered in patients who have two or more attacks per month that produce disability lasting 3 or more days per month; contraindication to, or failure of, acute treatments; use of abortive medication more than twice per week; and /or have uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction. • Recommended first-line agents for the prevention of migraine headache are propranolol, timolol, amitriptyline, divalproex sodium, and sodium valproate.

Clinical Guideline	Recommendation
American College of Cardiology (ACC) / European Society of Cardiology (ESC): **Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy (2003)**[67]	• β-Blockers are a preferred drug treatment strategy for symptomatic patients with outflow gradients present only with exertion. • Propranolol was the first agent used in the treatment of hypertrophic cardiomyopathy (HCM); more recently, extended release propranolol and other agents including atenolol, metoprolol, and nadolol are used. • There is no standardized consensus on the selection of medications for particular patients. The medication chosen for treatment is based largely on the preferences of individual practitioners, investigators, and centers. • For the initial medical treatment of exertional dyspnea, verapamil or a β-blocker may be used. Verapamil may be instituted in those who have failed β-blocker therapy or who have asthma. • Currently, there is no data demonstrating that using verapamil and a β-blocker concurrently offers any benefits compared to monotherapy with either agent. • Due to the potential for disopyramide to increase ventricular rate during AF, it is recommended to concurrently administer a low dose β-blocker to obtain a normal resting heart rate. • In patients with end-stage HCM, there is a lack of evidence demonstrating that β-blocker prevents or convey a benefit to congestive heart failure and ventricular systolic dysfunction, ultimately, these patients may become transplant candidates. • The use of β-blockers, verapamil or disopyramide for prophylaxis of symptoms in asymptomatic patients is still questionable. • β-Blockers or verapamil may be used to slow AV nodal conduction during the programming of a pacemaker. • There is a lack of data demonstrating the efficacy of β-blockers, verapamil and type IA antiarrhythmics for prophylaxis of sudden cardiac death (SCD) in asymptomatic HCM patients; an ICD is more effective at preventing SCD. • Management of sinus rhythm in patients with HCM is strongly recommended and β-blockers, verapamil and digoxin have proven to be effective in controlling heart rate in chronic AF.
American Academy of Neurology (AAN): **Practice Parameter: Therapies for essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology (2005)**[68]	• Propranolol and primidone are agents that are most commonly used to treat essential tremor (ET). • It is recommended that propranolol, propranolol LA, or primidone be offered to patients who want treatment for limb tremor in ET, depending on concurrent medical conditions and potential side effects. • It is recommended that either primidone or propranolol be used as initial therapy to treat limb tremor in ET. • It is recommended that atenolol and sotalol be considered for treatment of limb tremor associated with ET, and propranolol may be considered as a treatment option for head tremor in patients with ET. • Nadolol may be considered a treatment option for limb tremor associated with ET. • Pindolol is not recommended for treatment of limb tremor in ET. • Due to the lack of evidence, currently a recommendation regarding the use of metoprolol in the treatment of limb tremor in ET cannot be provided. • The combination of primidone and propranolol may be used to treat limb tremor when the use of a single agent does not adequately decrease tremor. • The dosages of propranolol and primidone may need to be increased after 12 months of therapy when treating limb tremor in ET.

III. Indications

Food and Drug Administration (FDA)-approved indications for β-adrenergic blocking agents are listed in Table 4. In addition, FDA-approved indications for specific arrhythmias are listed in Table 5. The differences in pharmacologic properties, including receptor affinity and membrane stabilization, allows for the individual agents to be used in and approved for a variety of indications. 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 Single Entity β-Adrenergic Blocking Agents[6-42]

Drug	Hyper-tension	Angina Pectoris†	Cardiac Arrhythmias‡	MI	HF	Pheo-chromo-cytoma	Migraine Prophylaxis	Hyper-trophic Subaortic Stenosis	Essential Tremor	Left Ventricular Dysfunction Following MI
Acebutolol	✔		✔							
Atenolol	✔	✔ §		✔ §§						
Betaxolol	✔									
Bisoprolol	✔									
Carvedilol	✔ ††				✔ ‖					✔ ¶
Carvedilol ER	✔ ††				✔ ‖					✔ ¶
Esmolol			✔							
Labetalol	✔ #									
Metoprolol succinate ER tablet	✔	✔			✔ *					
Metoprolol tartrate tablets	✔	✔		✔ §§						
Metoprolol tartrate injection				✔ §§						
Nadolol	✔	✔								
Nebivolol	✔									
Penbutolol	✔ ‡‡									
Pindolol	✔									
Propranolol tablets	✔	✔ ‖‖	✔	✔ ¶¶		✔ ##	✔ **	✔	✔	
Propranolol ER capsules (Inderal LA®)	✔	✔ ‖‖					✔ **	✔		
Propranolol ER tablets (InnoPran XL®)	✔									
Propranolol injection			✔							
Propranolol solution	✔	✔ ‖‖	✔	✔ ¶¶		✔ ##	✔ **	✔	✔	
Sotalol			✔							
Timolol	✔			✔ ¶¶			✔			

ER=extended-release, HF=heart failure, MI=myocardial infarction
† Long-term treatment.
‡ See Table 5 for the specific cardiac arrhythmias for which these particular agents are indicated.
§ Indicated for the long-term management of patients with angina pectoris due to coronary atherosclerosis.
‖ Indicated for the treatment of mild-to-severe HF of ischemic or cardiomyopathic origin and to reduce the risk of hospitalization.
¶ Indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of an MI and have a left ventricular ejection fraction ≤40% (with or without symptomatic HF).
# The IV formulation is indicated for control of blood pressure in severe hypertension.
* Indicated for the treatment of stable, symptomatic (New York Heart Association Class II or III) HF of ischemic, hypertensive or cardiomyopathic origin.
†† Indicated for the management of essential hypertension.
‡‡ Indicated in the treatment of mild to moderate hypertension.
§§ Indicated in clinically and/or hemodynamically stable patients with definite or suspected acute MI to reduce cardiovascular mortality.
‖‖ Indicated to decrease angina frequency and increase exercise tolerance in patients with angina pectoris due to coronary atherosclerosis.
¶¶ Indicated to reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable.
Indicated as an adjunct to alpha-adrenergic blockade to control BP and reduce symptoms of catecholamine secreting tumors.
** Indicated for the prophylaxis of common migraine headache.

Table 5. FDA-Approved Cardiac Arrhythmia Indications for the Single Entity β-Adrenergic Blocking Agents[6,11,17,18,20,26,35,38-41]

Indication	Acebutolol	Esmolol	Propranolol IR Tablets and Solution	Propranolol IV	Sotalol (Betapace®†)	Sotalol (Betapace AF®†)
Atrial fibrillation and rapid ventricular response			✔			
Digitalis-induced tachyarrhythmias				✔		
Intraoperative and postoperative tachycardia/hypertension		✔ §				
Maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter currently in sinus rhythm						✔
Premature ventricular contractions (PVCs)	✔			✔ ‖		
Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia				✔		
Ventricular arrhythmias/tachycardias				✔ ¶	✔ *	
Sinus tachycardia (noncompensatory)		✔				
Supraventricular arrhythmias/tachycardias		✔ ‡		✔ #		

† Betapace and Betapace AF are not interchangeable because of significant differences in labeling (i.e., patient package insert, dosing administration and safety information).
‡ Indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable.
§ Indicated for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated.
‖ Indicated for the treatment of persistent PVCs that impair the well-being of the patient and do not respond to conventional measures.
¶ With the exception of those induced by catecholamines or digitalis, propranolol is not the drug of first choice. In critical situations when cardioversion techniques or other drugs are not indicated or are not effective, propranolol may be considered.
# Indicated for the short-term treatment of supraventricular tachycardia, including Wolff-Parkinson-White syndrome and thyrotoxicosis, to decrease ventricular rate.
* Indicated for ventricular arrhythmias that, in the judgment of the physician, are life-threatening

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity β-adrenergic blocking agents (β-blockers) are summarized in Table 6. Each agent within the class possesses different pharmacokinetic properties. Since propranolol and metoprolol are predominantly metabolized via CYP450 2D6, it may be necessary to adjust the dose when starting or stopping a concomitant agent that inhibits this CYP450 enzymatic pathway.[13,17,29,30,35-37] Since atenolol is primarily excreted in the urine unchanged, it is necessary to adjust the dose in patients with reduced renal function.[7,21] Also, the lipophilic properties varies between the β-blocking agents; the lipophilic properties determines the extent of which the agent may penetrate across the blood brain barrier. The higher the lipid solubility of the agent, the higher the potential to cross the blood brain barrier and increase the risk of central nervous system adverse events, including dizziness and drowsiness.[1,2]

Table 6. Pharmacokinetic Parameters of the Single Entity β-Adrenergic Blocking Agents[1-42,66]

Drug	Systemic Bioavailability (%)	Protein Binding (%)	Lipid Solubility	Metabolism	Half-Life (hours)	Active Metabolites
Acebutolol	40	26	Low	Renal/ hepatic	3-4	Yes
Atenolol	50	6-16	Low	Renal	6-7	No
Betaxolol	84-93	~50	Low	Renal	14-22	No
Bisoprolol	80	~30	Low	Renal/hepatic	9-12	No
Carvedilol	25-35	98	Moderate	Hepatic (CYP2D6/2C9)	7-10	Yes
Carvedilol ER	21-30					
Labetalol	25	~50	Moderate	Hepatic	6-8	N/A
Metoprolol	50	12	Moderate	Hepatic (CYP2D6)	3-7	No
Metoprolol ER	50-77					
Nadolol	30	30	Low	Renal	20-24	No
Nebivolol	12-96	98	High	Hepatic (CYP2D6)	12	Yes
Penbutolol	80-98	~100	High	Hepatic	~5	N/A
Pindolol	>95	40	Moderate	Renal/hepatic	3-4	N/A
Propranolol	30	90	High	Hepatic (CYP2D6)	3-5	Yes
Propranolol ER	9-18				8-11	
Sotalol	90-100	0	Low	Renal	12	No
Timolol	75	<10	Low-Mod	Renal	4	No

ER=extended-release.
N/A=not available.

V. Drug Interactions

Significant drug interactions with the single entity β-adrenergic blocking agents (β-blockers) are listed in Table 7. All agents in this class block β_1 receptors, therefore common drug interactions with the β-blockers include any pharmacodynamic interaction with β_1 receptors. Since the nonselective agents also block β_2 receptors, there is the added risk of antagonistic effects with some pulmonary medications such as albuterol and salmeterol (β_2 receptor agonists). All of these agents can produce bradycardia and lead to arrhythmias if given in too high of a dose. This effect could be additive with other medications that reduce sinus conduction through the heart.[4] Pharmacokinetic interactions will vary as some of these agents are metabolized via the CYP 450 enzymatic system and others are renally excreted unchanged.[3]

Table 7. Significant Drug-Drug Interactions for the Single Entity β-Adrenergic Blocking Agents[4]

Drug(s)	Significance Level	Interaction	Mechanism
Acebutolol, atenolol, betaxolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol	1	Clonidine	Beta-blocker inhibition of β_2 receptor mediated vasodilation leaves peripheral α_2-receptor mediated vasoconstriction unopposed to clonidine stimulation.
Acebutolol, atenolol, betaxolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol	1	Verapamil	May be synergistic or additive effects. Verapamil may inhibit oxidative metabolism of certain β-blockers.
Nadolol, penbutolol, pindolol, propranolol, timolol	1	Epinephrine	Nonselective β blockade allows α -receptor effects of epinephrine to predominate. Increasing vascular resistance leads to a rise in blood pressure and reflex bradycardia.
Nadolol, penbutolol, pindolol,	1	Sympathomimetics (albuterol,	Nonselective β-blockers may block

Drug(s)	Significance Level	Interaction	Mechanism
propranolol, sotalol, timolol		arformoterol, bitolterol, formoterol, levoalbuterol, salmeterol)	the action of beta-agonists, potentially resulting in severe bronchospasm in asthmatics.
Pindolol, propranolol, sotalol	1	Phenothiazines (chlorpromazine, thioridazine)	Chlorpromazine may inhibit the first-pass hepatic metabolism of propranolol and increase its pharmacologic effects. Certain β-blockers may inhibit the metabolism of thioridazine.
Sotalol	1	Antihistamines, nonsedating (terfenadine)	Possibly additive risk of torsades de pointes.
Sotalol	1	Cisapride	Possibly additive prolongation of the QT interval.
Sotalol	1	Macrolides and related antibiotics (azithromycin, clarithromycin, erythromycin, telithromycin)	Possibly additive prolongation of the QT interval.
Sotalol	1	Quinolones (gatifloxacin, levofloxacin, moxifloxacin, ofloxacin)	Unknown. May increase risk of arrhythmias.
Sotalol	1	Ranolazine	Possibly additive prolongation of the QT interval.
Sotalol	1	Vardenafil	Unknown. May increase risk of arrhythmias.
Sotalol	1	Ziprasidone	Possibly synergistic or additive prolongation of the QT interval.
Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol	2	Non Steroidal Anti-inflammatory Drugs (NSAIDs), (ibuprofen, indomethacin, naproxen, piroxicam)	NSAIDs may inhibit renal prostaglandin synthesis, allowing unopposed pressor systems to produce hypertension.
Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol	2	Prazosin	Unknown.
Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol	2	Salicylates (aspirin, bismuth subsalicylate, magnesium salicylate, salsalate, sodium thiosalicylate)	Hypertension: salicylates may inhibit biosynthesis of prostaglandins involved in the antihypertensive activity of β-blockers. Heart failure: unknown.
Atenolol	2	Ampicillin	The bioavailability of atenolol may be decreased by impaired GI absorption induced by ampicillin.
Atenolol, metoprolol, pindolol, propranolol	2	Diltiazem	Possibly inhibition of oxidative metabolism of β-blockers and additive pharmacologic effects.
Atenolol, metoprolol, nadolol, pindolol, propranolol	2	Lidocaine	Reduced hepatic lidocaine metabolism and possibly a minor component of diminished hepatic blood flow.
Atenolol, metoprolol, propranolol, timolol	2	Quinidine	Oxidative metabolism of certain β-blockers may be inhibited by quinidine.

Drug(s)	Significance Level	Interaction	Mechanism
Atenolol, bisoprolol, metoprolol, propranolol	2	Rifamycins (rifabutin, rifampin, rifapentine)	Possibly due to increased hepatic metabolism from enzyme induction.
Carvedilol	2	Cyclosporine	Certain β-blockers may interfere with cyclosporine metabolism.
Carvedilol, propranolol	2	Digoxin	Carvedilol may increase digoxin bioavailability. Possible additive depression of myocardial conduction and decreased renal tubular digoxin secretion.
Carvedilol, labetalol, metoprolol, propranolol, timolol	2	Diphenhydramine	Inhibition of CYP2D6-mediated β-blocker metabolism.
Labetalol	2	Inhalation anesthetics (desflurane, enflurane, halothane, isoflurane, sevoflurane)	Additive myocardial depressant effects.
Metoprolol, propranolol	2	Barbiturates (amobarbital, butabarbital, butalbital, mephobarbital, pentobarbital, phenobarbital, primidone, secobarbital)	Barbiturates enhance enzyme induction and hepatic first-pass extraction that may reduce oral bioavailability of certain β-blockers.
Metoprolol, propranolol	2	Hydralazine	Hydralazine increases systemic availability of some β-blockers, probably by transient increase in splanchnic blood flow and decreasing first-pass hepatic metabolism.
Metoprolol, propranolol	2	Propafenone	Propafenone increases plasma β-blocker level by decreasing first-pass metabolism and reducing systemic clearance. Both drugs are oxidized by the hepatic cytochrome P450 system, and propafenone appears to inhibit the metabolism of the β-blocker.
Metoprolol, propranolol	2	Thioamines (methimazole, propylthiouracil)	Hyperthyroidism appears to cause increased clearance of β-blockers with a high extraction ration. This may be the result of increased liver blood flow, first-pass metabolism and volume of distribution.
Metoprolol, propranolol, timolol	2	Cimetidine	Cimetidine may reduce hepatic first-pass extraction, decrease liver blood flow, and inhibit hepatic metabolism of propranolol.
Nadolol, penbutolol, pindolol, propranolol, timolol	2	Ergot derivatives (Dihydroergotamine, ergotamine, methysergide)	Ergot alkaloid mediated vasoconstriction and β-blocker mediated blockade of peripheral β_2 receptors allows for unopposed ergot action.
Nadolol, penbutolol, pindolol, propranolol, timolol	2	Insulin	β-Blockers blunt sympathetic mediated responses to hypoglycemia.
Penbutolol, pindolol, propranolol, timolol	2	Theophyllines (aminophylline, dyphylline, oxtriphylline, theophylline)	Pharmacologic antagonism. B-blockers may reduce the n-demethylation of theophylline.

Drug(s)	Significance Level	Interaction	Mechanism
Propranolol	2	Rizatriptan	Inhibition of rizatriptan metabolism (monoamine oxidase-A) by propranolol is suspected.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

Significant adverse drug events with the single entity β-adrenergic blocking agents (β-blockers) are listed in Table 8. Some of the β-blockers have boxed warnings and these are listed in Tables 9-14. The most common side effects of the β-blockers are hypotension, dizziness, bradycardia and fatigue. Side effects may be reduced by slowly titrating the dose.[1,2,6-42,70-72] Patients with pulmonary dysfunction may have better tolerability with agents that are more cardioselective.[1,71,72]

Table 8. Adverse Drug Events (%) for the Single Entity β-Adrenergic Blocking Agents[6-10,12-25,27-42]

Adverse Event	Acebu-tolol	Aten-olol	Beta-xolol	Biso-prolol	Carve-dilol	Labe-talol	Meto-prolol	Nad-olol	Nebiv-olol	Penbu-tolol	Pin-dolol	Propran-olol*	Sotalol	Tim-olol
Cardiovascular														
Angina	-	-	-	-	2-6	-	-	-	✔	-	-	✔	-	✔
Arrhythmia	-	-	-	<1	-	-	-	1	✔	1-10	-	-	5	1
Arterial/vascular insufficiency/Raynaud's phenomenon	-	1-10	-	-	-	<1	1	2	-	<1	-	✔	<1	✔
Atrioventricular (AV) nodal disturbances	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Bradycardia	1-10	1-10	8†	1	2-10	<1	2-16	2‡	1	1†	≤2	6†	16	9
Cardiac failure/arrest	<2	-	-	-	-	<1	-	1	-	-	-	-	-	✔
Cardiogenic shock	-	-	-	-	-	-	✔	-	-	-	-	✔	-	-
Chest pain	2	1-10	<1	1-2	-	-	-	<1	1	2	3	2-4	16	1
Cold extremities	-	1-10	1-10	<1	-	-	1	1-10	-	-	≤2	✔	<1	✔
Congestive heart failure	1-10	1-10	1-10	<1	-	-	1	1	-	1-10	<1	✔	5	-
Edema	2	1-10	2	4	5-6	0-2	-	1-10	-	-	6	2	8	1
Electrocardiogram abnormal	-	-	-	-	-	-	-	-	-	-	-	-	7	-
Flushing	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Heart block	-	1-10	-	-	3	<1	5	-	-	<1	<2	-	-	✔
Hypertension	-	-	-	-	3	-	-	-	-	-	-	-	-	-
Hypotension	1-10	1-10	-	<1	9-20	1-5	1-27	1	-	<1	≤2	✔	6	✔
Myocardial contractility impaired	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Myocardial ischemia	-	-	-	-	<1	-	-	-	✔	-	-	-	-	-
Orthostatic hypotension	-	-	-	<1	-	-	-	<1	-	-	-	-	-	-
Palpitations	-	-	1-10	<1	1-10	-	1	1-10	-	-	≤1	-	14	✔
Peripheral circulation reduced	-	-	1-10	-	-	-	-	2	-	-	-	-	3	-
Peripheral edema	-	-	-	3	1-7	-	1	-	1	-	-	-	-	-
Postural hypotension	-	2	-	-	2	1	-	-	-	-	-	-	-	-
Rhythm disturbance	-	-	-	<1	-	-	-	1	-	-	-	-	-	-
Shortness of breath	-	-	-	-	-	-	3	-	1	-	-	-	-	-
Symptomatic bradycardia	-	-	1	-	-	-	-	-	-	-	-	-	-	-

Adverse Event	Acebu-tolol	Aten-olol	Beta-xolol	Biso-prolol	Carve-dilol	Labe-talol	Meto-prolol	Nad-olol	Nebiv-olol	Penbu-tolol	Pin-dolol	Propran-olol*	Sotalol	Tim-olol
Syncope	-	-	-	<1	3-8	<1	1	-	-	-	≤2	-	5	1
Tachycardia	-	-	-	-	-	-	-	-	-	-	≤2	-	-	-
Thrombosis, mesenteric arterial	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Central Nervous System														
Abnormal dreams	2	-	-	-	-	-	-	-	-	-	-	3	-	-
Amnesia	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Anxiety	1-10	-	-	<1	-	-	✔	-	-	-	≤2	-	4	✔
Catatonia	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Cerebral ischemia	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Cerebral vascular accident	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Change in behavior	-	-	-	-	-	-	-	1	-	-	-	-	-	-
Cognitive dysfunction	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Concentration decreased	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Confusion	-	1-10	-	<1	-	-	≥1	<1	-	-	-	✔	6	✔
Convulsions	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Depression	2	1-10	1	<1	<1	-	5	1-10	-	-	-	1-3	4	✔
Disorientation	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Dizziness	6	1-10	5	4	2-32	1-16	2-10	2	2-4	5	9	2-11	20	2
Drowsiness	-	1	>10	-	-	-	-	>10	-	-	-	2	-	-
Emotional lability	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Fatigue	11	1-10	3	6-8	4-24	1-10	1-10	2	2-5	4	8	3-17	20	3
Fever	-	-	-	-	3	-	-	-	-	-	-	-	-	-
Hallucinations	-	<1	-	<1	-	-	≥1	<1	-	-	<1	✔	-	✔
Headache	6	1-10	7	11	5-8	2	≥1	-	6-9	8	-	1-9	8	2
Hyper/hypoesthesia	1-10	-	-	1-2	1-10	-	-	-	-	-	-	-	-	-
Insomnia	3	1-10	>10	2-3	1-7	-	≥1	>10	1	2	10	3-8	-	✔
Lethargy	-	1-10	3	-	-	-	-	-	-	-	≤2	4	-	-
Lightheadedness	-	1	-	-	-	-	-	-	-	-	-	✔	12	-
Malaise	-	-	-	<1	1-10	-	-	-	-	-	-	-	-	-
Memory loss	-	-	-	<1	-	-	≥1	-	-	-	-	-	-	✔
Mental impairment	-	1-10	1-10	-	-	-	-	-	-	-	-	-	-	-
Migraine	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Nervousness	-	-	1	<1	-	-	✔	-	-	-	7	2	-	✔
Nightmares/vivid dreams	-	1-10	1	-	-	-	≥1	-	-	-	5	✔	-	✔
Paresthesia	-	-	-	<1	-	-	✔	1	≥1	-	-	-	-	1
Psychosis	-	<1	-	-	-	-	-	-	-	-	-	✔	-	-
Sedation	-	-	-	-	-	-	-	1	-	-	-	-	-	-

Adverse Event	Acebu-tolol	Aten-olol	Beta-xolol	Biso-prolol	Carve-dilol	Labe-talol	Meto-prolol	Nad-olol	Nebiv-olol	Penbu-tolol	Pin-dolol	Propran-olol*	Sotalol	Tim-olol
Sleep disturbance	-	-	-	<1	-	-	≥1	-	-	-	-	-	8	-
Somnolence	-	-	-	<1	2	-	≥1	-	-	-	-	✔	-	✔
Vertigo	-	2	-	<1	1-10	2	≥1	-	-	-	-	✔	<1	1
Dermatologic														
Acne	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Alopecia	-	<1	-	<1	-	<1	✔	-	-	-	-	✔	<1	✔
Cutaneous ulcers	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Dermatitis	-	-	-	<1	-	-	-	-	-	-	-	✔	-	-
Eczema	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Eczematous eruptions	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Erythema multiforme	-	-	-	-	<1	-	-	-	-	-	-	✔	-	-
Exfoliative dermatitis	-	-	-	-	<1	-	-	-	-	-	-	✔	-	-
Hyperkeratosis	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Nail changes	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Oculomucocutaneous reactions	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Photosensitivity	-	-	-	-	-	-	≥1	-	-	-	-	-	<1	-
Pruritus	1-10	-	-	<1	-	<1	5	-	-	-	1	✔	<1	1
Pseudopemphigoid	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Psoriasiform rash	-	<1	-	<1	-	-	-	-	-	-	-	✔	-	✔
Psoriasis (exacerbated)	-	-	-	<1	-	-	≥1	-	-	-	-	-	-	✔
Purpura	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Rash	2	-	1	<1	-	1	5	-	1	-	-	0-2	5	✔
Red crusted skin	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Scalp tingling	-	-	-	-	-	1-5	-	-	-	-	-	-	-	-
Skin necrosis after extravasation	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Stevens-Johnson syndrome	-	-	-	-	<1	-	-	-	-	-	-	✔	-	-
Sweating, excessive	-	-	-	1	-	-	✔	-	-	2	≤2	2	<1	-
Toxic epidermal necrolysis	-	-	-	-	<1	-	-	-	-	-	-	✔	-	-
Ulcers	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Urticaria	-	-	-	-	-	<1	✔	-	-	-	-	✔	5	✔
Endocrine and Metabolic														
Alkaline phosphatase increased	-	-	-	-	1-10	-	✔	-	-	-	<1	✔	-	-
Dehydration	-	-	-	-	2	-	-	-	-	-	-	-	-	-
Diabetes (exacerbated)	-	-	-	-	<1	-	≥1	-	-	-	-	-	-	-
Gout	-	-	-	<1	6	-	-	-	-	-	-	-	-	-
Hypercholesterolemia	-	-	-	-	4	-	-	-	≥1	-	-	-	-	-

Adverse Event	Acebu-tolol	Aten-olol	Beta-xolol	Biso-prolol	Carve-dilol	Labe-talol	Meto-prolol	Nad-olol	Nebiv-olol	Penbu-tolol	Pin-dolol	Propran-olol*	Sotalol	Tim-olol
Hyperglycemia	-	-	-	<1	5-12	-	-	-	-	<1	-	✔	-	-
Hyperkalemia	-	-	-	<1	3	-	-	-	-	-	-	✔	-	-
Hyperlipidemia	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Hypertriglyceridemia	-	-	-	<1	1	-	-	-	-	-	-	-	-	-
Hyperuricemia	-	-	-	-	1-10	-	-	-	≥1	-	-	-	-	-
Hypervolemia	-	-	-	-	2	-	-	-	-	-	-	-	-	-
Hypoglycemia	-	-	-	-	1-10	-	-	-	-	-	-	✔	-	-
Hypoglycemia masked	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Hyponatremia	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-
Libido decreased	-	-	-	-	-	-	≥1	-	-	-	-	-	-	1
Weight gain	-	-	-	-	-	-	-	-	-	-	<2	-	-	-
Gastrointestinal														
Abdominal discomfort	-	-	1-10	<1	-	-	-	1-10	-	-	4	-	-	-
Abdominal pain	1-10	-	-	-	-	-	1	-	≥1	-	-	1	-	-
Angioedema	-	-	-	<1	-	<1	-	-	-	-	-	-	-	✔
Anorexia	-	-	-	-	-	-	-	-	-	-	-	✔	-	✔
Constipation	4	1-10	1-10	<1	-	-	1	1-10	-	-	-	0-2	-	-
Cramping	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Diarrhea	4	1-10	1-10	3-4	1-12	-	5	1-10	2-3	3	≤2	2-7	7	✔
Dry mouth	-	-	-	1	-	-	1	-	-	-	-	-	-	✔
Dyspepsia	4	-	5	<1	-	1-4	-	-	-	3	-	1-7	-	1
Flatulence	3	-	-	-	-	-	1	-	-	-	-	4	2	-
Gastritis	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Gastrointestinal hemorrhage	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Heartburn	-	-	-	-	-	-	1	-	-	-	-	-	-	-
Ischemic colitis	-	-	-	-	-	-	-	-	-	<1	-	✔	-	-
Melena	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-
Nausea	4	1-10	1-10	2	2-9	0-19	1	1-10	1-3	4	5	1-6	10	1
Peptic ulcer	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Periodontitis	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-
Retroperitoneal fibrosis	-	-	-	-	-	-	✔	-	-	-	-	-	<1	✔
Stomach discomfort	-	-	-	-	-	-	-	-	-	-	-	✔	3-6	
Taste disorder	-	-	-	<1	-	1	✔	-	-	-	-	-	-	-
Vomiting	1-10	-	1-10	1-2	6	<1-3	≥1	1-10	-	-	≤2	✔	10	-
Weight gain	-	-	-	<1	10-12	-	✔	-	-	-	≤2	-	-	-
Genitourinary														
Cystitis	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Diabetes insipidus	-	-	-	-	-	<1	-	-	-	-	-	-	-	-

Adverse Event	Acebu-tolol	Aten-olol	Beta-xolol	Biso-prolol	Carve-dilol	Labe-talol	Meto-prolol	Nad-olol	Nebiv-olol	Penbu-tolol	Pin-dolol	Propran-olol*	Sotalol	Tim-olol
Dysuria	1-10	-	-	-	-	-	-	-	-	-	-	-	-	-
Ejaculatory failure	-	-	-	-	-	0-5	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	3	-	-	-	-	-	-	-	-	-
Impotence	1-10	1-10	1	<1	1-10	1-4	✔	-	-	1	≤2	1	2	✔
Interstitial nephritis	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Libido decreased	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Micturition (frequency)	3	-	-	-	-	-	-	-	-	-	-	1	-	-
Nocturia	1-10	-	-	-	-	-	-	-	-	-	-	-	-	-
Oliguria	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Pollakiuria	-	-	-	-	-	-	-	-	-	-	<2	-	-	-
Polyuria	-	-	-	<1	-	-	-	-	-	-	≤2	-	-	-
Proteinuria	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Sexual ability decreased	-	-	-	-	-	-	-	>10	-	-	-	-	3	-
Urinary incontinence	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Urinary retention	-	-	-	-	-	<1	-	-	-	-	-	-	-	-
Hematologic														
Agranulocytosis	-	-	-	-	-	-	✔	-	-	-	-	✔	-	-
Anemia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Aplastic anemia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Bleeding	-	-	-	-	-	-	-	-	-	-	-	-	2	-
Claudication	-	-	-	<1	-	-	≥1	-	-	-	≤2	-	-	✔
Eosinophilia	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Leukopenia	-	-	-	<1	<1	-	-	<1	-	-	-	-	<1	-
Pancytopenia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Prothrombin decreased	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-
Purpura	-	-	-	-	1-10	-	-	-	-	-	-	✔	-	-
Thrombocytopenia	-	<1	<1	<1	1-2	-	✔	<1	-	<1	-	✔	<1	-
Hepatic														
Cholestatic jaundice	-	-	-	-	<1	<1	✔	-	-	-	-	-	-	-
Hepatic necrosis	-	-	-	-	-	<1	-	-	-	-	-	-	-	-
Hepatitis	-	-	-	-	-	<1	✔	-	-	-	-	-	-	-
Increase liver enzymes	-	<1	-	-	-	-	-	-	-	-	7	-	-	-
Transaminases increase	-	-	-	<1	1-10	4	✔	-	-	-	-	✔	<1	-
Neuromuscular and Skeletal														
Arthralgia	2	-	3	1-10	6	-	✔	-	-	1-10	7	1	-	-
Arthritis	-	-	-	-	-	-	✔	-	-	-	-	-	-	-
Arthropathy	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Asthenia	-	-	-	≤2	-	-	-	-	-	-	-	-	-	-

Adverse Event	Acebu-tolol	Aten-olol	Beta-xolol	Biso-prolol	Carve-dilol	Labe-talol	Meto-prolol	Nad-olol	Nebiv-olol	Penbu-tolol	Pin-dolol	Propran-olol*	Sotalol	Tim-olol
Back pain	1-10	-	-	<1	2-7	-	-	-	-	-	-	-	3	-
Carpal Tunnel syndrome	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Extremity pain	-	-	-	-	-	-	-	-	-	-	-	-	7	-
Hyper/hypoesthesia	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Joint pain	1-10	-	-	-	-	-	-	-	-	-	7	-	-	-
Limb pain	-	-	-	-	-	-	-	-	-	2	-	-	-	-
Muscle cramps	-	-	-	<1	1-10	-	-	-	-	-	3	-	-	-
Muscle pain	-	-	-	<1	-	-	≥1	-	-	-	10	-	-	-
Myalgia	2	-	-	-	3	-	-	-	-	-	-	1	-	-
Myasthenia gravis exacerbated	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Myotonus	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Neuralgia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Paralysis	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Paresthesia	-	-	-	-	-	1-5	-	1	-	-	3	✔	4	1
Peripheral ischemia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Polyarthritis	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Restlessness	-	-	-	<1	1	-	-	-	-	-	-	-	-	-
Toxic myopathy	-	-	-	-	-	<1	-	-	-	-	-	-	-	-
Tremor	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Twitching	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Weakness	-	-	-	2	11	1	-	-	≥1	2	4	1	13	1
Ocular														
Abnormal/blurred vision	2	-	-	-	-	1	≥1	-	-	-	-	3	-	-
Burning	-	-	-	-	-	-	-	-	-	-	≤2	-	-	-
Conjunctivitis	1-10	-	-	-	-	-	-	-	-	-	-	-	-	-
Corneal sensitivity decrease	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Cystoid macular edema	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Diplopia	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Dry eyes	1-10	-	-	-	-	-	✔	-	-	-	-	-	-	✔
Eye discomfort	-	-	-	-	-	-	-	-	-	-	≤2	-	-	-
Eye irritation	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Eye pain	1-10	-	-	<1	-	-	-	-	-	-	-	-	-	-
Hyperemia of conjuctiva	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Keratitis	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Lacrimation, abnormal	-	-	-	<1	1-10	-	-	-	-	-	-	-	-	-
Mydriasis	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Ocular discharge	-	-	-	-	-	-	-	-	-	-	-	-	-	✔

Adverse Event	Acebu-tolol	Aten-olol	Beta-xolol	Biso-prolol	Carve-dilol	Labe-talol	Meto-prolol	Nad-olol	Nebiv-olol	Penbu-tolol	Pin-dolol	Propran-olol*	Sotalol	Tim-olol
Ocular pain	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Ptosis	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Refractive changes	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Visual acuity decreased	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Visual disturbances	-	-	-	<1	3-5	-	≥1	-	-	-	≤2	✔	5	✔
Xerophthalmia	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Otic														
Hearing decreased	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Tinnitus	-	-	-	<1	-	-	≥1	-	-	-	-	-	-	1
Renal														
Albuminuria	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blood urea nitrogen increase	-	-	-	<1	6	-	-	-	-	-	-	✔	-	-
Creatinine increase	-	-	-	<1	3	-	-	-	-	-	-	-	-	-
Glycosuria	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-
Kidney failure	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-
Renal colic	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Renal function abnormal	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-
Respiratory														
Asthma	-	-	-	-	<1	-	-	-	-	-	-	-	2	-
Bronchiolitis obliterans	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Bronchitis	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Bronchospasm	-	-	1-10	<1	<1	<1	1	1-10	-	<1	-	✔	-	1
Cough	1	-	-	3	5	-	-	-	-	2	-	1	-	✔
Dyspnea	4	<1	2	1-2	-	2	1-3	<1	-	2	5	1-6	21	1
Interstitial pneumonitis	-	-	-	-	<1	-	-	-	-	-	-	-	-	-
Laryngospasm	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Nasal congestion	-	-	-	-	1	1-6	-	-	-	-	-	-	-	✔
Nasopharyngitis	-	-	-	-	4	-	-	-	-	-	-	-	-	-
Pharyngitis	1-10	-	2	2	-	-	-	-	-	-	-	✔	-	-
Pulmonary edema	-	-	-	-	<1	-	-	-	-	-	-	✔	<1	✔
Rales	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Respiratory failure	-	-	-	-	-	-	-	-	-	-	-	✔	-	✔
Rhinitis	2	-	2	3-4	2	-	≥1	-	-	-	-	1	-	-
Sinus congestion	-	-	-	-	1	-	-	-	-	-	-	-	-	-
Sinusitis	-	-	-	2	-	-	-	-	-	-	-	-	-	-
Upper respiratory infection	-	-	3	5	-	-	-	-	-	3	-	5	5-8	-
Wheezing	1-10	<1	-	-	-	-	1	-	-	-	≤2	✔	-	-
Miscellaneous														

Adverse Event	Acebu-tolol	Aten-olol	Beta-xolol	Biso-prolol	Carve-dilol	Labe-talol	Meto-prolol	Nad-olol	Nebiv-olol	Penbu-tolol	Pin-dolol	Propran-olol*	Sotalol	Tim-olol
Allergy	-	-	-	-	1-10	-	-	-	-	-	-	-	-	✔
Anaphylactoid reaction	-	-	-	-	1	<1	-	-	-	-	-	✔	-	-
Cutaneous vasculitis	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Gangrene	-	-	-	-	-	-	✔	-	-	-	-	-	-	-
Hyperphosphatemia	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	<1	-	-	-	-	-	-	-	-
Injury	-	-	-	-	3-6	-	-	-	-	-	-	-	-	-
Lactate dehydrogenase increased	-	-	-	-	-	-	✔	-	-	-	<1	-	-	-
Leukocytoclastic vasculitis	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Lupus syndrome	-	<1	-	-	-	<1	-	-	-	-	-	✔	-	✔
Mesenteric arterial thrombosis	-	-	-	-	-	-	-	-	-	<1	-	-	-	-
Peyronie's disease	-	<1	-	<1	-	<1	<1	-	-	-	-	✔	-	✔
Positive antinuclear antibody test	-	<1	-	<1	-	<1	-	-	-	-	-	-	-	-
Sudden death	-	-	-	-	1-10	-	-	-	-	-	-	-	-	-
Uric acid increased	-	-	-	<1	-	-	-	-	-	-	<1	-	-	-

*When percentage figures given for propranolol, figures are derived from InnoPran XL prescribing information (PI), and from comparative trials with acebutolol (PI), betaxolol (PI), penbutolol (PI), and labetalol (PI).
†Defined as <50 beats/min.
‡ Defined as <40 beats/min; bradycardia with heart rates <60 beats/min (definition of bradycardia by American Heat Association) is common with this agent.
- Event not reported or incidence <1%.
✔ Percent not specified.

Table 9. Black Box Warning for Atenolol[5,21]

WARNING
Cessation of Therapy with Atenolol: Patients with coronary artery disease, who are being treated with atenolol, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta-blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta-blockers, when discontinuation of atenolol is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that atenolol tablet, USP be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol tablet, USP, therapy abruptly even in patients treated only for hypertension.

Table 10. Black Box Warning for Metoprolol[5,13,29,30]

WARNING
Ischemic Heart Disease*: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, metoprolol administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol therapy abruptly even in patients treated only for hypertension.

*Applies to both metoprolol succinate and tartrate

Table 11. Black Box Warning for Nadolol[5,14,31]

WARNING
Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction has occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Table 12. Black Box Warning for Propranolol[37]

WARNING
Angina Pectoris*: There have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without a physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it is usually advisable to reinstitute propranolol therapy and take other measures appropriate for the management of angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

*Indicated as a Black Box Warning in the InnoPran XL package insert, but only indicated as a warning in package inserts of the other formulations.

Table 13. Black Box Warning for Sotalol[5,18,40,41]

WARNING
Arrhythmias: To minimize the risk of induced arrhythmia, patients initiated or re-initiated on sotalol hydrochloride tablets (AF) should be placed for a minimum of three days (on their maintenance dose) in a facility that can provide cardiac resuscitation, continuous electrocardiographic monitoring and calculations of creatinine clearance. For detailed instructions regarding dose selection and special cautions for people with renal impairment, see DOSAGE AND ADMINISTRATION. Sotalol is also indicated for the treatment of documented life-threatening ventricular arrhythmias and is marketed under the brand name BETAPACE®. BETAPACE®, however, should not be substituted for sotalol hydrochloride tablets (AF) because of significant differences in labeling (i.e., patient package insert, dosing administration and safety information).

Table 14. Black Box Warning for Timolol[5,19,42]

WARNING
Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

VII. Dosing and Administration

The usual dosing regimens for the single entity β-adrenergic blocking agents (β-blockers) are summarized in Table 15. Dosing of the β-blockers may vary according to the indication. Adverse effects and heart rate determine dose limits. Drug interactions which increase or decrease β-blocker serum levels and patient pharmacokinetic differences (such as rapid metabolizers, and reduced liver and/or renal function) will impact the goal dose of any agent. Below is the standard dosing of these medications for the indication specified.

Table 15. Dosing and Administration for the Single Entity β-Adrenergic Blocking Agents[6-10,12-25,27-42]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Acebutolol	Hypertension: Initial: 400 mg/day, twice-daily dosing may be required for adequate control Maintenance: 200 to 1,200 mg/day in two divided doses; optimal response usually in 400 to 800 mg/day range Maximum: 1,200 mg/day Ventricular arrhythmias: Initial: 200 mg twice daily Maintenance: gradual increase until optimal response, usually 600 to 1,200 mg/day Maximum: 1,200 mg/day Elderly: Lower maintenance doses required; maximum 800 mg/day Hepatically/renally impaired: Creatinine clearance (Cr_{Cl}) <50 mL/min: reduce dose by 50% Cr_{Cl} <25 mL/min: reduce dose by 75% Hepatic impairment: use caution	Safety and efficacy for use in pediatric patients have not been established.	Capsule: 200 mg 400 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Discontinuation of therapy should occur gradually over 2 weeks.		
Atenolol	Angina pectoris: Tablet: Initial: 50 mg once daily Maintenance: if optimal response not achieved after 1 week, increase to 100 mg daily Maximum: 200 mg/daily Acute myocardial infarction: Intravenous (IV): 5 mg injection over 5 minutes followed by another 5 mg injection 10 minutes later Oral: after IV dose, 50 mg twice daily, or 100 mg once daily for 6 to 9 days or until hospital discharge Hypertension: Tablet: Initial: 50 mg once daily Maintenance: if optimal response not achieved, increase dose to 100 mg once daily Maximum effective dose: 100 mg/day Elderly/renally impaired: Cr_{Cl} 15-35 mL/min: maximum 50 mg daily Cr_{Cl} <15 mL/min: maximum 25 mg daily Withdrawal of therapy should occur gradually.	Safety and efficacy for use in children have not been established.	Injection: 5 mg/10 mL Tablet: 25 mg 50 mg 100 mg
Betaxolol	Hypertension: Initial: 10 mg once daily Maintenance: if optimal response not seen after 7 to 14 days, may increase the dose to 20 mg daily Maximum: 40 mg/day; doses above 20 mg have not shown significance benefit, but doses of up to 40 my have been studied and well tolerated. Renally impaired (severe): Initial: 5 mg once daily Maintenance: may increase by 5 mg increments every 2 weeks up to 20 mg daily Maximum 20 mg/day Discontinuation of therapy should occur gradually over 2 weeks.	Safety and efficacy for use in children have not been established.	Tablet: 10 mg 20 mg
Bisoprolol	Hypertension: Initial: 5 mg once daily Maintenance: if optimal control is not achieved, dose may be increased to 10 mg daily and again to 20 mg daily if needed Maximum: 20 mg/day Another antihypertensive agent may be added Elderly: Dose adjustment not required	Safety and efficacy for use in children have not been established.	Tablet: 5 mg 10 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hepatically/renally impaired (Cr_{Cl} ≤40 mL/min): Initial: 2.5 mg daily and titrate carefully		
Carvedilol	Heart Failure: Capsule, extended-release: Initial: 10 mg once daily Maintenance: if tolerated, double the dose at intervals of >14 days as needed up to 80 mg once daily Maximum: 80 mg/day Tablet: Initial: 3.125 mg twice daily Maintenance: if tolerated, double the dose at intervals of >14 days as needed up to 50 mg twice daily Maximum: 100 mg/day Hypertension: Capsule, extended-release: Initial: 20 mg once daily Maintenance: if tolerated, double the dose every 7 to 14 days as needed up to 80 mg once daily Maximum: 80 mg/day Tablet: Initial: 6.25 mg twice daily Maintenance: if tolerated, double the dose every 7 to 14 days as needed up to 25 mg twice daily Maximum: 50 mg/day Left ventricular dysfunction following myocardial infarction: Capsule, extended-release: Initial: 20 mg once daily Maintenance: if tolerated, double the dose every 3 to 10 days as needed up to 80 mg once daily; usual dose 10 to 80 mg once daily Maximum: 80 mg/day Tablet: Initial: 6.25 mg twice daily Maintenance: if tolerated, double the dose every 3 to 10 days as needed up to 25 mg twice daily Maximum: 50 mg/day Severe hepatic impairment: Carvedilol therapy is contraindicated in these patients Discontinuation of therapy should occur gradually over 1 to 2 weeks.	Safety and efficacy for use in children have not been established.	Capsule, extended-release: 10 mg 20 mg 40 mg 80 mg Tablet: 3.125 mg 6.25 mg 12.5 mg 25 mg
Labetalol	Hypertension: Tablet: Initial: 100 mg twice daily Maintenance: titrate by 100 mg twice daily every 2 to 3 days, usual dose is 200 to 400 mg twice daily; larger doses may be administered three times daily to improve tolerability Maximum: doses of 1,200 to 2,400 mg daily have been used	Safety and efficacy for use in children have not been established.	Injection (disposable syringe): 5 mg/mL Tablet: 100 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	IV: Repeated injection: Initial: 20 mg over 2 minutes Maintenance: additional 40 to 80 mg injections at 10-minutes intervals may be given up to a total of 300 mg Maximum: 300 mg Infusion: Initial: 1 mg/mL solution at 2 mL/min, or 2 mg/3 mL solution at 3 mL/min; Maintenance: adjust infusion rate until satisfactory response 50 to 200 mg) Maximum: 300 mg Inpatient transfer to oral dosing from IV: Initial: 200 mg, followed by an additional 200 to 400 mg 6 to 12 hours later Maintenance: 200 mg twice daily, then titrate by 200 mg twice daily in 1-day intervals up to 1,200 mg twice daily Maximum: 2,400 mg/day <u>Elderly</u>: Tablet: Initial: 100 mg twice daily Maintenance: titrate by 100 mg twice daily as needed; usual dose is 100 to 200 mg twice daily Maximum: not specified <u>Hepatic Impairment:</u> Use with caution Discontinuation of therapy should occur gradually over 1 to 2 weeks.		200 mg 300 mg
Metoprolol	<u>Angina pectoris</u>: Tablet: Initial: 100 mg/day in divided doses Maintenance: gradually increase dose in weekly intervals up to 400 mg/day; usual dose is 100 to 400 mg/day Maximum: 400 mg/day Tablet, extended-release: Initial: 100 mg once daily Maintenance: gradually increase dose in weekly intervals up to 400 mg/day Maximum: 400 mg/day <u>Congestive heart failure</u>: Tablet, extended-release: New York Heat Association Class II: Initial: 25 mg/day, double the dose every 2 weeks up to 200 mg/day or highest dose tolerated Maximum: 200 mg/day	Hypertension (≥6 years of age) Tablet, extended release: Initial: 1 mg/kg once daily (max: 50 mg/dose) Maintenance: adjust dose to optimal response up to 2 mg/kg or 200 mg/day Maximum: 2 mg/kg daily (max: 200 mg/day)	Injection: (ampule, vial, syringe): 1 mg/mL Tablet: 25 mg 50 mg 100 mg Tablet, extended-release: 25 mg 50 mg 100 mg 200 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	More severe heart failure: Initial: 12.5 mg/day, double the dose every 2 weeks up to 200 mg/day or highest dose tolerated Maximum: 200 mg/day <u>Hypertension</u>: Tablet: Initial: 100 mg/day in single or divided doses Maintenance: gradually increase dose in weekly intervals up to 450 mg/day; usual dose is 100 to 450 mg/day Maximum: 450 mg/day Tablet, extended-release: Initial: 25 to 100 mg once daily Maintenance: gradually increase dose in weekly intervals up to 400 mg/day Maximum: 400 mg/day <u>Myocardial infarction</u>: Early treatment: IV: Initial: 3 IV bolus injections of 5 mg at 2 minute intervals Maintenance: if IV tolerate, give 50 mg every 6 hours for 48 hours starting 15 minutes after last IV dose, then continue 100 mg twice daily Late treatment: Tablet: Initial: 100 mg twice daily Maintenance: 100 mg twice daily for at least 3 months <u>Hepatic Impairment:</u> Use with caution Discontinuation of therapy should occur gradually over 1 to 2 weeks.		
Nadolol	<u>Angina pectoris</u>: Initial: 40 mg once daily Maintenance: Increase dose by 40 to 80 mg every 3 to 7 days until optimal response up to 240 mg daily Maximum: 240 mg/day <u>Hypertension</u>: Initial: 40 mg once daily Maintenance: Increase dose gradually by 40 to 80 mg increments until optimal response up to 320 mg daily Maximum: 320 mg/day <u>Renal impairment:</u> Cr_{Cl} >50 mL/min: administer dose every 24 hours Cr_{Cl} 31-50 mL/min: administer dose every 24 to 36 hours Cr_{Cl} 10-30 mL/min: administer dose every 24 to 48 hours Cr_{Cl} <10 mL/min: administer dose every 40 to 60 hours	Safety and efficacy for use in children have not been established.	Tablet: 20 mg 40 mg 80 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Discontinuation of therapy should occur gradually over 1 to 2 weeks.		
Nebivolol	Hypertension: Initial: 5 mg once daily Maintenance: Increase in 2 week intervals until optimal response Maximum: 40 mg/day Renal impairment: Cr_{Cl} <30mL/min: 2.5 mg daily and titrate cautiously if necessary Moderate hepatic impairment: 2.5 mg daily and titrate cautiously if necessary Discontinuation of therapy should occur gradually over 1 to 2 weeks.	Safety and efficacy for use in children have not been established.	Tablet: 2.5 mg 5 mg 10 mg
Penbutolol	Hypertension: Initial: 20 mg once daily Maintenance: 20 mg once daily; usual dose 10 to 40 mg once daily Maximum: 80 mg/day Discontinuation of therapy should occur gradually over 1 to 2 weeks.	Safety and efficacy for use in children have not been established.	Tablet: 20 mg
Pindolol	Hypertension: Initial: 5 mg twice daily Maintenance: after 3 to 4 weeks, may be increase by 10 mg/day increments as needed up to 60 mg/day Maximum: 60 mg/day Impaired renal or hepatic function: Use with caution Discontinuation of therapy should occur gradually over 1 to 2 weeks.	Safety and efficacy for use in children have not been established.	Tablet: 5 mg 10 mg
Propranolol	Angina pectoris: Capsule, extended-release (LA): Initial: 80 mg once daily Maintenance: may gradually increase dose in 3 to 7 days increments up to 160 mg once daily or higher; usual dose is 160 mg daily Maximum: 320 mg/day Tablet, oral solution: Maintenance: 80 to 320 mg/day administered in two, three or four divided doses Maximum: 320 mg/day Atrial fibrillation: Tablet, oral solution: Maintenance: 10 to 30 mg in three to four divided doses before meals and at bedtime	Safety and efficacy for use in children have not been established.	Capsule, extended-release (InnoPran XL®): 80 mg 120 mg Capsule, long-acting (Inderal LA®): 60 mg 80 mg 120 mg 160 mg Injection

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Cardiac arrhythmias: IV: Initial: 1 to 3 mg administered at 1 mg/min, and if necessary, a second dose may be given after 2 minutes of up to a maximum of 5 mg; additional doses should be given within 4 hours Essential tremor: Tablet, oral solution: Initial: 40 mg twice daily Maintenance: usual dose is 120 mg/day Maximum: 320 mg/day Hypertension: Capsule, extended-release (Inderal LA®): Initial: 80 mg once daily Maintenance: may titrate dose up to 120 mg daily or higher; usual dose is 120 to 160 mg daily Maximum: 640 mg/day Capsule, extended-release (InnoPran XL®): Initial: 80 mg once daily at bedtime (around 10 pm) Maintenance: may titrate dose up to 120 mg daily Maximum: 120 mg/day Tablet, oral solution: Initial: 40 mg twice daily Maintenance: gradually increase the dose up to 640 mg daily; usual dose is 120 to 240 mg/day divided into two to three doses Maximum: 640 mg/day Hypertrophic subaortic stenosis: Capsule, extended-release (Inderal LA®): Maintenance: 80 to 160 mg once daily Tablet, oral solution: Usual: 20 to 40 mg three to four times daily before meals and at bedtime Migraine prophylaxis: Capsule, extended-release (Inderal LA®): Initial: 80 mg once daily Maintenance: may increase dose gradually up to 160 to 240 mg once daily; usual dose is 160 to 240 mg once daily; if optimal response does not occur after 4 to 6 weeks of therapy at max dose, propranolol should be discontinued Maximum: 240 mg/day Tablet, oral solution: Initial: 80 mg daily in divided doses Maintenance: increase dose gradually up to 160 to 240 mg/day; if optimal response does not occur after 4 to 6 weeks of therapy at max dose, propranolol should be discontinued Maximum: 240 mg/day		(ampule/ vial): 1 mg/mL Oral solution: 20 mg/5 mL 40 mg/5 mL Tablet: 10 mg 20 mg 40 mg 60 mg 80 mg 90 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Myocardial infarction: Tablet, oral solution: Initial: 40 mg three times daily Maintenance: after 1 month, titrate up to 60 to 80 mg three times daily as tolerated; usual dose is 180 to 240 mg in divided doses Maximum: 240 mg/day Pheochromocytoma: Tablet, oral solution: Operable tumors: 60 mg/day in divided doses for 3 days preoperatively as adjunct to alpha-adrenergic blockade Inoperable tumors: 30 mg/day in divided doses as adjunct to alpha-adrenergic blockade Impaired renal or hepatic function: Use with caution IV use should be reserved for life-threatening arrhythmias or those occurring under anesthesia. Discontinuation of therapy should occur gradually over several weeks.		
Sotalol	Maintenance of normal sinus rhythm: Tablet, AF: Initial: 80 mg twice daily Maintenance: increase dose gradually with 3 days between increments up to 120 to 160 mg twice daily, carefully monitor QT interval and renal function; decrease dose if QT ≥ 520 msec Maximum: 320 mg/day Renally impaired (maintenance of sinus rhythm): Tablet, AF: Cr_{Cl} >60 mL/min: Administer every 12 hours Cr_{Cl} 40-60 mL/min: Administer every 24 hours Cr_{Cl} <40 mL/min: Use is contraindicated Ventricular arrhythmias: Tablet, Initial: 80 mg twice daily Maintenance: increase dose gradually with 3 days between increments up to 120 to 160 mg twice daily Maximum: 480 to 640 mg/day; use high doses only with life-threatening refractory ventricular arrhythmias Renally impaired (ventricular arrhythmias): Cr_{Cl} >60 mL/min: Administer every 12 hours Cr_{Cl} 30-60 mL/min: Administer every 24 hours Cr_{Cl} 10-30 mL/min: Administer every 36 to 48 hours Cr_{Cl} <10 mL/min: Individualize dose Sotalol should be initiated and doses increased in a hospital with facilities for cardiac rhythm monitoring and assessment. Before starting sotalol, previous antiarrhythmic therapy should generally be withdrawn under careful monitoring for a	Ventricular arrhythmias (≤2 years of age): Dose is based on age and dose reduction factor Ventricular arrhythmias (>2 years of age): Tablet Initial: 30 mg/m^2 three times daily Maintenance: increase dose gradually with 3 days between increments up to 60 mg/m^2 three times daily Maximum: 60 mg/m^2 three times daily Tablet, AF: Safety and efficacy for use in children have not been established.	Tablet: 80 mg 120 mg 160 mg 240 mg Tablet, AF: 80 mg 120 mg 160 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	minimum of 2 to 3 plasma half-lives if the patient's clinical condition permits. Discontinuation of therapy should occur gradually over 1 to 2 weeks.		
Timolol	Hypertension: Initial: 10 mg twice daily Maintenance: increase dose gradually in 7 day increments up to 60 mg/day; usual dose is 20 to 40 mg/day Maximum: 60 mg/day divided into 2 doses Migraine prophylaxis: Initial: 10 mg twice daily Maintenance: may increase dose up to 30 mg/day Maximum: 30 mg/day divided into 2 doses Myocardial infarction: Maintenance: 10 mg twice daily Impaired hepatic or renal function: Dose reductions may be necessary in these patients If satisfactory response is not reached after 6 to 8 weeks at the maximum daily dosage, timolol should be discontinued. Discontinuation of therapy should occur gradually over 1 to 2 weeks.	Safety and efficacy for use in children have not been established.	Tablet: 5 mg 10 mg 20 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity β-adrenergic blocking agents (β-blockers) are summarized in Table 16.

Table 16. Dosing and Administration for the Single Entity β-Adrenergic Blocking Agents

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypertension				
Dahlöf et al[73] STOP-Hypertension Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs placebo	DB, MC, RCT Swedish men and women 70-84 years old with treated or untreated essential hypertension defined as SBP ≥180 mm Hg with a DBP of ≥90 mm Hg, or DBP >105 mm Hg irrespective of the SBP measured on 3 separate occasions during a 1-month placebo run-in phase in previously untreated patients	N=1,627 25 months	Primary: Frequency of stroke, myocardial infarction and other cardiovascular death Secondary: Not reported	Primary: The active treatments significantly reduced the number of all primary endpoints (94 vs 58; RR, 0.60; 95% CI, 0.43 to 0.85; *P*=0.0031), frequency of stroke (53 vs 29; RR, 0.53; 95% CI, 0.33 to 0.86; *P*=0.0081) and frequency of other cardiovascular deaths (13 vs 4; RR, 0.30; 95% CI, 0.07 to 0.97; *P* value not reported) compared to placebo. There was not a statistically significant decrease observed in the rate of myocardial infarction between the active treatments and placebo (28 vs 25; RR, 0.87; 95% CI, 0.49 to 1.56; *P* value not reported). Secondary: Not reported
Dhakam et al[74] Atenolol 50 mg QD vs nebivolol 5 mg QD vs placebo QD	DB, RCT, XO Never-treated subjects with isolated systolic hypertension	N=16 17 weeks	Primary: Change in central blood pressure Secondary: Change in peripheral blood pressure, AIx, aPWV and N-terminal proBNP.	Primary: There was not a statistically significant difference observed in the change in aortic SBP between the nebivolol and atenolol groups (125±3 vs 127±3 mm Hg; *P*=0.4), but both agents were significantly better than placebo (131±2 mm Hg; *P* value not reported). There was not a statistically significant difference observed in the change in aortic DBP between the nebivolol and atenolol groups (75±2 vs 73±2 mm Hg; *P*=0.3), but both agents were better than placebo (82±2 mm Hg; *P* value not reported). Secondary: There was not a statistically significant difference observed in the change in brachial SBP between the nebivolol and atenolol groups (136±3 vs 137±3 mm Hg; *P*=0.4), but both agents were significantly better than placebo (149±3 mm Hg; *P* value not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was not a statistically significant difference observed in the change in brachial DBP between the nebivolol and atenolol groups (75±2 vs 73±2 mm Hg; *P*=0.5), but both agents were better than placebo (82±2 mm Hg; *P* value not reported). There was a statistically significant reduction in AIx in the atenolol group compared to the nebivolol group (32±2 vs 28±2%; *P*=0.4), but both agents were significantly better than placebo (22±2%; *P* value not reported). There was not a statistically significant difference observed in the reduction of aPWV in the atenolol group compared to the nebivolol group (8.9±0.3 vs 9.1±0.3 m/s; *P*=0.2), but both agents were significantly better than placebo (10.0±0.4 m/s; *P* was not reported). There was not a statistically significant difference observed in the rise in N-terminal pro-BNP in the atenolol group compared to the nebivolol group (157 vs 138 pg/mL; *P*=0.6), but both agents were significantly better than placebo (75 mg/mL; *P* value not reported).
Fogari et al[75] Atenolol 50 mg QD vs nebivolol 5 mg QD There was a 4-week run-in period on placebo	DB, PG, RCT Patients 18-70 years of age with stable NIDDM (HgA_{1c} ≤8% during previous 6 months with diet and/or oral therapy stable for ≥ 6 months), and mild to moderate hypertension (DBP ≥95 and <116 mm Hg) at the end of the 4-week run-in period with placebo	N=30 6 months	Primary: Changes in blood pressure, heart rate, 24-hour urinary C-peptide excretion, HbA_{1c}, plasma glucose, and lipid levels Secondary: Euglycemic hyperinsulinemic clamp test (body glucose utilization)	Primary: Both atenolol and nebivolol significantly reduced blood pressure and heart rate from baseline (*P*<0.001 for all measures), but there was not a significant difference between the treatment groups at weeks 0, 2 and 24 (*P*>0.05 for all measures). There no significant changes from baseline in mean 24-hour urinary C-peptide excretion, HbA_{1c}, plasma glucose, and lipid levels (*P*>0.05). There were also no significant differences observed between treatment groups in any of these measures (*P*>0.05). Secondary: There was not a significant decrease from baseline in mean values for whole body glucose utilization observed in neither the atenolol group nor the nebivolol group (mean decrease of 0.9% vs 2.6%, respectively; *P*>0.05) and the groups were significant from each other (*P*>0.05).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mazza et al[76] Amlodipine 5 to 10 mg QD vs nebivolol 2.5 to 5 mg QD There was a 4-week single-blind run-in period	DB, MC, PG, RCT Patients between 65-89 years of age with mild to moderate essential hypertension and DBP ranging from 95-114 mm Hg	N=168 16 weeks	Primary: Changes of sitting blood pressure and response rates Secondary: Standing blood pressure changes, and standing and sitting heart rate changes	Primary: There was not a significant difference observed between the amlodipine and nebivolol treatments groups in changes in sitting DBP (blood pressure values and *P* values not reported). At weeks 4 and 8, a slightly lower sitting SBP was observed in per-protocol patients in the amlodipine groups vs those in the nebivolol group (blood pressure values not reported, *P*<0.005). Response rates were not significantly difference between the amlodipine group and the nebivolol group (86% vs 88%, respectively; *P* value not reported). The percentage of patients who reached normalization (blood pressure <140/90 mm Hg) was no significant between the amlodipine and the nebivolol groups (47% vs 50%; *P* value not reported). Secondary: There were significant differences in standing blood pressure observed between the groups (*P* value not reported); with the exception of S blood pressure which was lower in the amlodipine group at week 8 (*P* value not reported). Heart rate was significantly lower in the nebivolol group compared to the amlodipine group at all treatment visits (*P*<0.001). Patients in the amlodipine group experienced a significantly greater rate of headache (7 vs 5 patients) and ankle edema (12 vs 0 patients) compared to the patients in the nebivolol group (*P*<0.05 for both).
Czuriga et al[77] NEBIS Bisoprolol 5 mg QD vs nebivolol 5 mg QD	MC, PG, RCT, SB Patients 30-65 years with mild to moderate hypertension, a DBP 95-110 mm Hg and a SBP ≤180 mm Hg at the end of the placebo run-in period who were either newly diagnosed or	N=273 16 weeks	Primary: Percentage of responders achieving DBP normalization (≤90 mm Hg) or a DBP reduction of at least 10 mm Hg and heart sitting rate	Primary: There was not a significant difference between percentage of responders between the nebivolol group (92%) and the bisoprolol group (89.6%; *P* value not reported). There was not a significant difference in the mean change in blood pressure observed between the nebivolol and bisoprolol (SBP: −20.5±12.9 vs −20.0±12.0 mm Hg, respectively; *P*=0.7434) and DBP (−15.7±6.4 vs −16.0 ± 6.8 mm Hg, respectively; *P*=0.8230).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
There was a 4-week placebo run-in period	previously treated hypertensives and required a change of therapy in consequence of side-effects or poor compliance.		Secondary: Adverse events and symptom questionnaire	There was not a significant difference in mean heart rate observed between the nebivolol (68.7 ± 8.5 per minute) and the bisoprolol group (68.1 ± 7.5 per minute; *P* value not reported). Secondary: There was not significant difference in rates of adverse events reported between the nebivolol (8 patients [5.8%]) and the bisoprolol group (12 patients [8.9%]; *P*>0.05). All adverse events were either mild (55%) or moderate (45%) in intensity. Both treatments demonstrated a significant reduction in the basal score index at visit 5 (nebivolol −0.7±1.7 vs bisoprolol −0.5±1.3; *P*<0.02 compared to baseline), but there was no significant difference between treatment groups (*P*>0.05).
Rosei et al[78] Lisinopril 20 mg QD vs nebivolol 5 mg QD There was a 4-week antihypertensive drug washout period	DB, MC, PG, RCT Patients between 24 and 65 years with mild to moderate uncomplicated essential hypertension that was newly diagnosed, or previous antihypertensive therapy was withdrawn at >1 month before active treatment, and had a sitting DBP of >95 and <114 mmHg.	N=65 12 weeks	Primary: Response rates and changes in sitting blood pressure Secondary: Standing blood pressure and sitting and standing heart rate	Primary: There was not a significant difference in response rates observed between the two treatment groups. Both treatment groups significantly reduced sitting SBP (*P*<0.0001) and DBP (*P*<0.0001) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits (*P* values not reported), but at week 8, DBP was significantly lower in the nebivolol group compared to the lisinopril group (*P*<0.05). Secondary: There was not a significant difference observed between treatment groups in standing blood pressure measurements (*P* values not reported). Both treatment groups significantly reduced sitting heart rate (*P*<0.01) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits (*P* values not reported), but at week 8, heart rate were significantly lower in the nebivolol group compared to the lisinopril group (*P*<0.05).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Van Bortel, Bulpitt et al[79] Losartan 50 mg QD vs nebivolol 5 mg QD There was a single-blind 2-week placebo run-in phase. If after 6 weeks, DBP was not normalized, then HCTZ 12.5 mg QD was added to therapy	DB, MC, PG, RCT Patients less than 70 years of age with DBP at randomization between 95 and 114 mm Hg	314 12 weeks	Primary: Effects on blood pressure and overall QOL Secondary: Comparison of different aspects of QOL	Primary: At the end of 12 weeks, both nebivolol and losartan significantly reduced SBP compared to baseline (*P*<0.0001 for both), but the agents were not significantly different from each other (*P* value not reported). Both agents also significantly decreased DBP compared to baseline (*P*<0.0001), but nebivolol significantly reduced DBP compared to losartan (*P*<0.02). At the end of 12 weeks, both nebivolol and losartan significantly improved QOL scores compared to baseline (*P*<0.007), but the agents were not significantly different from each other (*P* value not reported). Secondary: At week 12 there was not a significant difference observed in the individual questions of the QOL questionnaire between the groups (*P* values not reported). Questions inquired about headaches, lightheadedness, sleepiness, flushing, and sexual function.
Frick et al[80] Penbutolol 40 mg BID vs propranolol 160 mg BID	DB, XO Patients 29-64 years old with hypertension and WHO classes I and II	N=20 13 weeks	Primary: blood pressure and heart rate Secondary: Not reported	Primary: Penbutolol significantly reduced supine and standing blood pressures (both SBP and DBP) from baseline (*P*<0.05). Propranolol also significantly reduced blood pressures from baseline (SBP: *P*<0.02 and diastolic: *P*<0.01), but there was not significant difference between agents (*P* value not reported). Penbutolol significantly reduced supine and standing heart rates from baseline (from 76±10 to 61±9; *P*<0.001 and from 85±13 to 67±8; *P*<0.001, respectively. Propranolol also significantly reduced heart rates from baseline (to 59±8; *P*<0.001 and to 63±7; *P*<0.001, respectively), but there was not significant difference between agents (*P* value not reported). Secondary: Not reported
Davidov et al[81] Betaxolol 10 to 40 mg QD	DB, MC, RCT Patients 21-73 years with	N=141 24 weeks	Primary: Change in blood pressure and heart	Primary: Both betaxolol and propranolol significantly reduced SBP from baseline (7±2.5 and 7±2.0 mm Hg; *P*<0.01 for both).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs propranolol 40 to 160 mg BID	mild to moderate hypertension (supine DBP of 95-115 mm Hg)		rate Secondary: Not reported	Both betaxolol and propranolol significantly reduced DBP from baseline (11±0.9 and 9±1.2 mm Hg; *P*<0.01 for both). Both betaxolol and propranolol significantly heart rate from baseline (6±1.3 and 7±1.1 bpm; *P*<0.01 for both). At the end of the study, there was not a significant difference in response between groups (*P* values were not reported). Secondary: Not reported
Reim et al[82] Acebutolol 400 mg QD vs propranolol 160 mg QD	DB, MC, XO Patients 18-70 years with essential hypertension and blood pressure of >150/90 mm Hg	N=18 14 weeks	Primary: blood pressure and heart rate during ergometer exercise test Secondary: Not reported	Primary: There was not a significant difference observed between the acebutolol and propranolol groups in decreases in blood pressure (systolic and diastolic) and heart rate at rest (*P*=0.123, *P*=0.230 and *P*=0.210, respectively). At the ergometer 25 watt load, heart rate and DBP were not significantly different between acebutolol and propranolol (*P*=0.087 and *P*=0.068, respectively), but SBP was significantly lower in the acebutolol group (*P*=0.042) At the higher ergometer loads of 50 and 75 watts, acebutolol had a significantly lower increase in SBP and heart rate compared to propranolol during exercise (50 watts: *P*=0.004 and *P*=0.012, respectively; 75 watts: *P*=0.005 and *P*=0.001, respectively), but there was not a significant difference observed between the groups in DBP in the 50 and 75 watt loads (*P*=0.057 and *P*=0.058, respectively). At the highest ergometer load of 100 watts, acebutolol significantly reduced systolic and DBPs and heart rate compared to propranolol (*P*=0.003, *P*=0.001, and *P*=0.001, respectively). Secondary: Not reported
Saunders et al[83]	DB, PG	N=153	Primary:	Primary:

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Labetalol 100 to 800 mg BID vs propranolol 40 to 320 mg	Patients with mild to moderate hypertension	Duration not specified	Blood pressure and heart rate Secondary: Not reported	Labetalol was significantly better than propranolol at the end of monotherapy at lowering DBP (*P*<0.05) but there was no difference in lowering SBP. Propranolol was significantly better at lowering heart rate compared to labetalol (*P*<0.01). No difference in the decrease in blood pressure after a diuretic was added. Secondary: Not reported
Stoschitzky et al[84] Bisoprolol 10 mg once on day 1, then 5 mg QD vs carvedilol 50 mg once on day 1, then 25 mg BID vs nebivolol 10 mg once on day 1, then 5 mg QD	DB, PC, RCT, XO Male patients between 22 and 34 years with a height between 177 and 189 cm, and body weight between 66 and 86 kg	N=16 1 week	Primary: Heart rate and blood pressure at rest and exercise Secondary: Effects on nocturnal melatonin release and QOL	Primary: Compared to baseline, heart rate at exercise was decreased at 3 hours after the first dose by bisoprolol (–24%), carvedilol (–17%) and nebivolol (–15%); (*P*<0.05 for each group). Bisoprolol was significantly better than nebivolol (*P*<0.05). Compared to baseline, heart rate at exercise was decreased at 24 hours after the first dose by bisoprolol (–18%), carvedilol (12 hours; –15%) and nebivolol (–13%); (*P*<0.05 for each group). There was not a statistical significance observed between the groups. Compared to baseline, heart rate at exercise was decreased at 24 hours after the respective last dose at the end of 1 week of chronic administration by bisoprolol (–14%), carvedilol (12 hours; –15%) and nebivolol (–13%); (*P*<0.05 in all cases). There was not a statistical significance observed between the groups. All of the agents significantly decreased SBP both at rest and exercise at 3 and 24 h after the first dose as well at 24 h after the last dose after 7 days of chronic administration (*P*<0.05 in all cases). None of the agents had a significant effect on DBP at rest or at exercise (*P* values not reported). Secondary: Compared to placebo, nocturnal melatonin release was decreased by

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				bisoprolol (–44%, *P*<0.05) whereas nebivolol (-16%) and carvedilol (–19%) had no effect (*P* value not reported). Total QOL with carvedilol (8.0±0.8) was slightly but significantly lower than that with placebo (8.6±0.4), nebivolol (8.5±0.6) and bisoprolol (8.4±0.5); (*P*<0.05 in all cases).
VA Cooperative Study[85] Propaserp group: Propranolol 40-160 mg TID (P), propranolol 40-160 mg TID plus HCTZ 35 mg (P+T), propranolol 40-160 mg TID plus hydralazine 35 mg (P+H) or propranolol 40-160 mg TID plus HCTZ 35 mg plus hydralazine 35 mg (P+T+H) vs Hydrazide group: Reserpine 35 mg plus HCTZ 35 mg (R+T)	DB, RCT Men 18-59 years with DBP of 90-114 mm Hg	N=450 18 months	Primary: Percent of patients who achieved a DBP <90 mm Hg at 6 months, heart rate and withdrawal rate Secondary: Not reported	Primary: At 6 months, significantly more patients in the R+T arm (88%) attained a DBP <90 mm Hg and at least 5 mm Hg less than the initial blood pressure compared to the P arm (52%; *P*<0.01) and the P+H arm (72%; *P*<0.05). The other arms: P+T (81%) and P+T+H (92%) were not significantly different than the R+T arm (*P* values not reported). The 12 and 18 month results do not have the statistical validity of the 6 month results due to the reduced sample size. The following percentage of patients attained DBP <90 mm Hg and at least 5 mm Hg less than the initial pressure: R+T=89.1% and 82.6%, P=59.5 and 58.1%, P+T=86.0 and 86.4%, P+H=67.4 and 76.1%, and P+T+H=89.4 and 91.8%; *P* values not reported. There was not a significance difference in heart rate reductions at 6 months and 18 months between the groups (R+T=5.0±1.3 and 5.0±1.3 mean change in heart rate, P=9.1±1.3 and 9.2±1.8, P+T=8.8±1.2 and 6.3±1.5, P+H=8.9±1.3 and 7.8±1.5, and P+T+H=5.9±1.1 and 7.7±1.5; *P* values not reported). Withdrawals for any reason were similar between the treatment arms and were not statistically significant (R+T=14 patients, P=11, P+T=12, P+H=14, and P+T+H=16; *P* values not reported). Secondary: Not reported
Black et al[86] CONVINCE Active control group:	DB, MC, RCT Patients ≥55 years with at least 1 other established risk factor for	N=16,602 3 years	Primary: Acute myocardial infarction, stroke, or cardiovascular disease-related	Primary: There was not a statistically significant difference observed in the occurrence of myocardial infarctions (133 vs 166 patients, respectively; HR, 0.82; 95% CI, 0.65 to 1.03; *P*=0.09), fatal or nonfatal stroke (133 vs 118 patients, respectively; HR, 1.15; 95% CI,

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atenolol 50 mg or HCTZ 12.5 mg QD vs COER verapamil 180 mg QD	cardiovascular, in addition to hypertension.		death Secondary: Expanded cardiovascular disease, all-cause mortality, cancer, hospitalization for bleeding, incidence of primary end points occurring between 6 AM and noon	0.90 to 1.48; *P*=0.26) or cardiovascular disease-related death, (152 vs 143, respectively; HR, 1.09; 95% CI, 0.87 to 1.37; *P*=0.47) between the COER verapamil group and the active control group. Secondary: There was not a statistically significant difference observed in the occurrence of expanded cardiovascular diseases (793 vs 775 patients, respectively; HR, 1.05; 95% CI, 0.95 to 1.16; *P*=0.31), all-cause mortality (337 vs 319 patients, respectively; HR, 1.08; 95% CI, 0.93 to 1.26; *P*=0.32), cancer (310 vs 299, respectively; HR, 1.06; 95% CI, 0.91 to 1.24; *P*=0.46), or in incidence of primary endpoints occurring between 6 AM and noon (99 vs 88, respectively; HR, 1.15; 95% CI, 0.86 to 1.53; *P*=0.34) between the COER verapamil group and the active control group. There was a statistically significant difference in occurrence of hospitalizations for bleeding (118 vs 79 patients, respectively; HR, 1.51; 95% CI, 1.15 to 2.04; *P*=0.003), between the COER verapamil group and the active control group.
Hannson, Hedner et al[87] NORDIL <u>Conventional group:</u> β-blocker, diuretic, or both vs diltiazem 180 to 360 mg QD Specific β-blockers and diuretics used in the study were not specified	BE, MC, OL, RCT Patients 50-74 with DBP of ≥100 mm Hg on 2 occasions, and were previously untreated, or if previously treated, patients could be included if they had blood pressure ≥100 mm Hg at 2 consecutive visits, at least 1 week apart, during a run-in period when no antihypertensive treatment was given.	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, myocardial infarction and other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal myocardial infarction	Primary: There was not a statistically significant difference observed in the occurrence of the combined primary endpoint between the diltiazem group compared to the conventional group (403 vs 400 patients, respectively; RR, 1.00; 95% CI, 0.87 to 1.15; *P*=0.97). Secondary: There were significantly fewer occurrences of fatal plus nonfatal stroke in the diltiazem group (159 patients) compared to the conventional group (196 patients; RR, 0.80; 95% CI, 0.65 to 0.99; *P*=0·04). There was not statistically significant difference observed in the occurrence of fatal plus nonfatal myocardial infarctions between the diltiazem group and the conventional group (183 vs 157 patients, respectively; RR, 1.16; 95% CI, 0.94 to 1.44; *P*=0.17).
Hannson, Lindholm et al[88]	BE, MC, OL, RCT	N=6,614	Primary: Combined fatal	Primary: The combined fatal mortality endpoints occurred in 221of the 2,213

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
STOP-2 Conventional drug group Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs Newer drug group ACE inhibitors: enalapril 10 mg QD or lisinopril 10 mg QD or calcium antagonists: felodipine 2.5 mg QD, or isradipine 2-5 mg QD	Swedish men and women between 70-84 years old with treated or untreated essential with hypertension on 3 separate occasions defined by systolic pressure ≥180 mm Hg, diastolic pressure >105 mm Hg, or both	60 months	stroke, myocardial infarction and other fatal cardiovascular disease, and combined fatal and nonfatal stroke, myocardial infarction and other cardiovascular mortality Secondary: Not reported	patients in the conventional drugs group and in 438 of 4,401 in the newer drugs group (RR, 0.99; 95% CI, 0.84 to 1.16; *P*=0.89). The combined fatal and nonfatal mortality endpoints occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (RR, 0.96; 95% CI, 0.86 to 1.08; *P*=0.49). Secondary: Not reported
Messerli et al[89] β-Blockers (atenolol, metoprolol, pindolol) vs diuretics (amiloride, chlorthalidone, HCTZ, HCTZ-triamterene or thiazide)	MA Ten randomized trials lasting ≥1 year, which used as first line agents diuretics and/or b-blockers, and reported morbidity and mortality outcomes in patients ≥60 years with hypertension	N=16,164 1 year	Primary: cardiovascular morbidity and mortality and all-cause morbidity Secondary: Not reported	Primary: Diuretic treatment significantly reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI, 0.64 to 0.87), while β-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI, 0.78 to 1.23; *P* values not reported). Diuretic treatment significantly reduced the odds for all-cause mortality by 14% (OR, 0.86; 95% CI, 0.77 to 0.96) while β-blockers did not reduce all-cause mortality (OR, 1.05; 95% CI, 0.88 to 1.25; *P* values not reported). Secondary: Not reported
Van Bortel, Fici et al[90] Nebivolol	MA Twelve randomized	N=2,653 Varied among	Primary: Antihypertensive effect and	Primary: Overall, higher response rates were observed with nebivolol than all the other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs active comparator (ARB, β-blocker, CCB, or ACE inhibitor) or placebo	controlled studies involving ≥ 25 patients with essential hypertension where nebivolol 5 mg QD was compared to placebo or other active drugs for ≥ 1 month	studies	tolerability Secondary: Not reported	to 1.73; *P*=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; *P*=0.001) but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; *P*=0.283), CCBs (OR, 1.19; 95% CI, 0.83 to 1.70; *P*=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; *P*=0.212). Overall, a higher percentage of patients obtained normalized blood pressure with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; *P*=0.012). A higher percentage of patient taking nebivolol obtained normalized blood pressure compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; *P*=0.004), and CCBs (OR, 1.96; 95% CI, 1.05 to 1.96; *P*=0.024), but when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; *P*=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; *P*<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; *P*=0.482). In comparing nebivolol to the groups individually, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; *P*=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; *P*=0.007) and CCBs (OR, 0.49; 95% CI 0.33 to 0.72; *P*<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08; *P*=0.127). Secondary: Not reported
Wiysonge et al[91] β-Blocker therapy (atenolol, metoprolol, oxprenolol, propranolol) vs other antihypertensive	MA Thirteen randomized controlled trials evaluating men and nonpregnant women, aged 18 years and over, with hypertension as defined by cutoff points	N=91,561 Varied among studies	Primary: All cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, and adverse	Primary: There was not a statistically significant difference observed in all cause mortality between the β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; *P* value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; *P* value not reported), and RAS inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; *P* value not reported). There was a statistically significant higher rate in all cause mortality with β-blocker therapy compared to CCB therapy (RR, 1.07; 95% CI, 1.00 to 1.14; *P*=0.04).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapies (i.e., placebo, diuretic, calcium channel blocker, or renin-angiotensin system inhibitors)	operating at the time of the study under consideration		drug reactions.	Secondary: There was a statistically significant decrease in stroke seen with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a statistically significant increase in stroke with β-blocker therapy compared to CCBs (RR, 1.24; 95% CI, 1.11 to 1.40) and RAS inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53], but there was no difference found compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09; *P* values not reported). CHD risk was not significantly different between β -blockers and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), a diuretic (RR, 1.12; 95% CI, 0.82 to 1.54), a CCB (RR, 1.05; 95% CI, 0.96 to 1.15), or an RAS inhibitor (RR, 0.90; 95% CI, 0.76 to 1.06; *P* values not reported). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97]. The effect of β-blockers on cardiovascular disease was significantly worse than that of CCBs (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28), or RAS inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3; *P* values not reported). There was a statistically significant higher rate of discontinuation of therapy due to side effects with β-blocker compared to those on diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and RAS inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference with CCBs (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported; *P* values not reported.
Lindholm et al[92] β-Blockers (atenolol, metoprolol, oxprenolol, pindolol, propranolol) vs other antihypertensive	MA Thirteen randomized controlled trials evaluating the treatment of primary hypertension with a β-blocker as first-line treatment (in at least 50% of all patients in one	N=105,951 2.1-10 years	Primary: Stroke, myocardial infarction and all-cause mortality Secondary: Not reported	Primary: The relative risk of stroke was 16% higher for β-blockers than for the comparator drugs (RR, 1.16; 95% CI, 1.04 to 1.30; *P*=0.009). The relative risk of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15% to 38%; *P*<0.0001). The relative risk of myocardial infarction was 2% higher for β-blockers than for the comparator drugs (RR, 1.02; 95% CI, 0.93 to

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapies (amiloride, amlodipine, bendro-flumethiazide, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan, verapamil) or placebo	treatment group) and outcome data for all-cause mortality, cardiovascular morbidity, or both			1.12), which was not statistically significant (*P* value not reported). The relative risk of all-cause mortality was 3% higher for β-blockers than for the comparator drugs (RR, 1.16; 95% CI, 0.99 to 1.08; *P*=0.14). Secondary: Not reported
Congestive Heart Failure				
CIBIS Investigators and Committees[93] CIBIS Bisoprolol 1.25 to 5 mg QD vs placebo All patient received standard therapy (diuretic and vasodilator)	DB, MC, PC, PG, RCT Patients 18-75 years with NYHA functional class III or IV due to idiopathic dilated cardiomyopathy, ischemia, hypertension or valvular heart disease, a LVEF of <40%, and background therapy with a diuretic and a vasodilator	N=641 1.9 years	Primary: Total mortality Secondary: Tolerability and analysis critical events	Primary: There was no statistical significance between bisoprolol and placebo in total mortality (53 vs 67; RR, 0.80; 95% CI, 0.56 to 1.15; *P*=0.22). Secondary: Bisoprolol was well tolerated with no between group difference in premature treatment withdrawals (82 on placebo, 75 on bisoprolol; not significant; *P* value not reported). Significantly fewer patients in the bisoprolol group required hospitalization for cardiac decompensation (90 in placebo versus 61 in bisoprolol; *P*<0.01), and more patients improved by at least one NYHA functional class (48 on placebo versus 68 on bisoprolol; *P*=.04) by the end of follow-up period.
CIBIS-II Investigators and Committees[94] CIBIS-II Bisoprolol 1.25 to 10 mg QD added to usual therapy (diuretic and vasodilator)	DB, MC, PC, RCT Symptomatic patients 18-80 years in NYHA class III or IV, with LVEF of 35% or less receiving standard therapy with diuretics and ACE inhibitor or other	N=2,647 1.3 years	Primary: All-cause mortality Secondary: All-cause hospital admissions, cardiovascular mortality, cardiovascular	Primary: CIBIS-II was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit. All-cause mortality was significantly lower with bisoprolol than on placebo (156 [11.8%] vs 228 [17.3%] deaths, respectively; HR, 0.66; 95% CI, 0.54 to 0.81; *P*<0.0001). Significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3.6%] vs 83 [6.3%] deaths, respectively; HR,

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	vasodilator		mortality and cardiovascular hospital admissions (composite endpoint) and permanent premature treatment withdrawals	0.56; 95% CI, 0.39 to 0.80; *P*=0.0011). Secondary: All-cause hospital admissions was significantly lower with bisoprolol than on placebo (440 [33%] vs 513 [39%] patients, respectively; HR, 0.80; 95% CI, 0.71 to 0.91; *P*=0.0006). All- cardiovascular deaths was significantly lower with bisoprolol than on placebo (119 [9%] vs 161 [12%] patients, respectively; HR, 0.71; 95% CI, 0.56 to 0.90; *P*=0.0049). Occurrence of composite endpoints of all cardiovascular deaths and cardiovascular admissions was significantly lower with bisoprolol than on placebo (388 [29%] vs 463 [35%] patients, respectively; HR, 0.79; 95% CI, 0.69 to 0.90; *P*=0.0004). Occurrence of treatment withdrawals was not statistically different between bisoprolol and the placebo group (194 [15%] vs 192 [15%] patients, respectively; HR, 1.00; 95% CI, 0.82 to 1.22; *P*=0.98).
MERIT-HF Study Group[95] MERIT-HF Metoprolol CR/XL 12.5 mg up to 200 mg QD vs placebo	DB, MC, PC, RCT Symptomatic patients 40-80 years in NYHA class II-IV, with LVEF of 40% or less stabilized on standard therapy (diuretic and vasodilator)	N=3,991 1 year	Primary: All-cause mortality and all-cause mortality in combination with all-cause admission to hospital (time to first event) Secondary: Not reported	Primary: Study was stopped early on the recommendation of the independent safety committee. All-cause mortality was significantly lower in the metoprolol CR/XL group than in the placebo group (145 [7.2%] vs 217 [11.0 %] deaths, RR, 0.66; 95% CI, 0.53 to 0.81; *P*=0.00009). There were significantly fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs 132; RR, 0.59; 95% CI, 0.45 to 0.78; *P*=0.0002) and deaths from worsening heart failure (30 vs 58; RR, 0.51; 95% CI, 0.33 to 0.79; *P*=0.0023). Study drug was permanently stopped early in 13.9% of the patients in the metoprolol CR/XL group and in 15.3% of patients in the placebo group (RR, 0.90; 95% CI, 0.77 to 1.06). Secondary: Not reported
Packer, Coats et al[96]	DB, MC, PC, RCT	N=2,280	Primary:	Primary:

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Carvedilol 3.125 to 25 mg BID vs placebo	Patients with severe chronic heart failure as a result of ischemic or nonischemic cardiomyopathy, dyspnea or fatigue at rest or on minimal exertion for ≥2 months and a LVEF <25% despite appropriate conventional therapy with diuretics, and an ACE inhibitor, or ARB	10.4 months	Total mortality Secondary: Combined risk of death or hospitalization for any reason and withdrawal rates	The study was stopped early due to statistical significance. The annual mortality in the placebo group was 19.7% (190) versus 12.8% (130 deaths) in the carvedilol group, a 35% reduction in mortality (95% CI, 19 to 48%; *P*<0.00013). Secondary: Carvedilol reduced the combined risk of death or hospitalization for any reason by 24% compared to placebo (425 vs 507 patients; 95% CI, 13 to 33%; *P*<0.001) Withdrawal rates were significantly higher in the placebo group compared to the carvedilol group (18.5 vs 14.8; *P*=0.02).
Dargie HJ[97] CAPRICORN Carvedilol 6.25 to 25 mg bid mg vs placebo	DB, MC, PC, RCT Patients 18 years and older with a stable myocardial infarction occurring 3 to 21 days prior to randomization, LVEF ≤40% and ACE inhibitor therapy for ≥48 hours	N=1,959 1.3 years	Primary: All-cause mortality, and all-cause mortality or cardiovascular hospital admissions Secondary: Sudden death, hospital admission for heart failure, recurrent nonfatal myocardial infarction, and all-cause mortality or recurrent nonfatal myocardial infarction.	Primary: There was not a significant difference observed between the carvedilol and placebo groups in the combined endpoint of all-cause mortality and hospital admissions due to cardiovascular events (340 [35%] vs 367 [37%], respectively; HR, 0.92; 95% CI, 0.80 to 1.07; *P*=0.296). All-cause mortality alone was statistically better in the carvedilol group than the placebo group (116 [12%] vs 151 [15%], respectively; HR, 0.77; 95% CI, 0.60 to 0.98; *P*=0.031). Secondary: There was not a significant difference observed between the carvedilol and placebo groups in sudden death (51 [5%] vs 69 [7%], respectively; HR, 0.74; 95% CI, 0.51 to 1.06; *P*=0.098) or in hospital admissions for heart failure (118 [12%] vs 138 [14%], respectively; HR, 0.86; 95% CI, 0.67 to 1.09; *P*=0.215). The carvedilol group, compared to placebo, experienced significantly lower rates of nonfatal myocardial infarctions (34 [3%] vs 57 [6%], respectively; HR, 0.59; 95% CI, 0.39 to 0.90; *P*=0.014) and all-cause mortality or recurrent nonfatal myocardial infarction (139 [14%] vs 192 [20%], respectively; HR, 0.71; 95% CI, 0.57 to 0.89; *P*=0.002).
Bristow et al[98]	DB, MC, PC, RCT	N=345	Primary: Submaximal	Primary: There were no differences on submaximal exercise with any dose

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Low dose group: Carvedilol 6.25 mg BID vs Medium dose group: Carvedilol 12.5 mg BID vs High dose group: Carvedilol 25 mg BID vs placebo All patients remained on their standard medications	Symptomatic (≥3 months) patients, 18-85 years with stable heart failure from ischemic or nonischemic dilated cardiomyopathy, an LVEF of ≤35%, a 6-minute walk test between 150 to 425 m and on stable doses of diuretics and ACE inhibitors for 2 weeks before baseline testing	6 months	exercise improvement Secondary: Minnesota questionnaire, changes in NYHA functional class, changes in LVEF, hospitalization, and changes in signs and symptoms of heart failure, occurrence of adverse clinical experiences and survival	compared to placebo. Walk distances between in each group ranged between 300 to 400 m in both the 6-minute and 9-minute walk tests; *P*=0.50 and *P*=0.27, respectively). Secondary: There were no significant changes in the overall Minnesota Questionnaire scores incorporating both physical and emotional dimensions (changes from baseline in the placebo and low-, medium-, and high-dose carvedilol groups of –7.3, –7.9, –7.3, and –6.6, respectively; *P*=0.512 in difference from placebo). There were no significant improvements in NYHA functional classes in the carvedilol groups compared to placebo (actual values not reported; *P*=0.64). Carvedilol treatment resulted in a dose-related significant improvement in LVEF; carvedilol 6.25 mg (~5 EF units; *P*<0.005), 12.5 mg (~6 EF units; *P*<0.005) and 25 mg (~7.5 EF units; *P*<0.0001) compared to placebo (2 EF unit improvement). The mean number of hospitalizations per patient were significantly reduced in each of the carvedilol groups (~0.1 hospitalizations) compared to placebo (~0.35; *P*<0.01). Bradycardia was significantly higher in the carvedilol 12.5 mg group (10 [11%]) and the 25 mg group (10 [11%]) compared to placebo (1 [1%]; *P*<0.05). Also, dizziness was significantly higher in the carvedilol 25 mg group (34 [38%]) compared to the placebo group (19 [23%]; *P*<0.05). The clinical significance of these advents was not mentioned. There was a dose-related, statistically significant reduction in mortality in the carvedilol-treated groups, with respective mortality rates of 6.0% for the carvedilol 6.25 mg group (RR, 0.356; 95% CI, 0.127 to 0.998; *P*<0.05), 6.7% for the 12.5 mg group (HR, 0.416; 95% CI, 0.158 to 1.097; *P*=0.07), and 1.1% in the 25 mg group (HR, 0.067; 95% CI, 0.009 to 0.512; *P*<0.001) compared to 15.5% mortality in the

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo group. Combining all three carvedilol arms of the study compared to the placebo arm showed statistical significance in all-cause mortality, risk reduced by 73% (*P*<0.001).
Lechat et al[99] β-Blockers (bisoprolol, bucindolol, carvedilol, metoprolol, and nebivolol) vs placebo	MA Eighteen double-blind, placebo-controlled, randomized trials with β-blockers for NYHA I-IV chronic heart failure	N=3,023 1.5-15 months	Primary: All-cause mortality, hospitalizations due to heart failure, combination of all-cause mortality and hospitalizations for worsened heart failure, changes in functional status and changes in LVEF Secondary: Not reported	Primary: All endpoints showed a significant effect for β-blockers (*P*<0.05). β-Blockers demonstrated a 32% reduction in risk of death compared to placebo (130 vs 156 deaths; 95% CI, 12% to 47%; *P*=0.003). β-Blockers demonstrated a 41% reduction in hospitalizations due to heart failure compared to placebo (166 vs 223 hospitalizations; 95% CI, 26% to 52%; *P*<0.001). β-Blockers demonstrated a 37% reduction in the combination of mortality and morbidity compared to placebo (239 vs 293; 95% CI, 24% to 49%; *P*<0.001). β-Blockers demonstrated a 32% increase in the likelihood of improvement in NYHA class (95% CI, 1% to 74%; *P*=0.04) and a 30% decrease in the likelihood of worsening NYHA (95% CI, 4% to 50%; *P*=0.03) compared to placebo β-Blockers demonstrated a 29% increase in ejection fraction compared to placebo (0.23±0.04 vs 0.31±0.04; $P<10^{-9}$). β-adrenergic agents did not differ in respect to any outcome measure except that reduction in mortality risk. Beta selective agents were less robust than the nonselective agents (*P*=0.049). Secondary: Not reported
Brophy et al[100] β-Blockers (bisoprolol, bucindolol, carvedilol,	MA Twenty-two randomized trials evaluating the	N=10,135 3-23 months	Primary: Overall mortality and hospitalizations for CHF	Primary: β-Blockers significantly reduced mortality compared to placebo (444 vs 624; OR, 0.65; 95% CI, 0.53 to 0.80).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metoprolol and nebivolol) vs placebo	comparison of β-blockers and placebo in patients with CHF of various etiologies		Secondary: Not reported	β-Blockers significantly reduced hospitalizations due to CHF compared to placebo (540 vs 754; RR, 0.64; 95% CI, 0.53 to 0.79). The probability that β-blocker therapy reduced total mortality and hospitalizations for congestive heart failure was almost 100%. The best estimates of these advantages are 3.8 lives saved and 4 fewer hospitalizations per 100 patients treated in the first year after therapy. The probability that these benefits are clinically significant (>2 lives saved or >2 fewer hospitalizations per 100 patients treated) is 99%. Secondary: Not reported
Whorlow et al[101] β-Blockers (bisoprolol, bucindolol, carvedilol metoprolol, nebivolol) vs placebo	MA Eighteen studies evaluating the comparison of β-blockers and placebo in patients with NYHA class IV heart failure currently taking background therapy (ACE inhibitors and diuretics with or without digoxin)	N=8,119 (NYHA IV only=589) 3-21 months	Primary: Mortality in NYHA class IV patients Secondary: Not reported	Primary: β-Blockers demonstrated a 29% reduction in mortality compared to placebo in patients with NYHA class IV (RR, 0.71; 95% CI, 0.52 to 0.96; *P* value not reported). The 29% risk reduction is similar to risk reduction seen with β-adrenergic blockers in other NYHA classes (*P* value not reported). β-Blockers demonstrated a 32% reduction in mortality compared to placebo in patients with NYHA I-IV (HR, 0.68; 95% CI, 0.61 to 0.77; *P* value not reported). Secondary: Not reported
Bouzamondo et al[102] β-Blockers (bisoprolol, bucindolol, carvedilol, and metoprolol) vs placebo	MA Randomized controlled evaluating patients with heart failure depending on NYHA class	N=not specified Duration varied	Primary: Overall mortality and hospitalized for worsening heart failure Secondary: Not reported	Primary: β-Blockers reduced overall mortality by 22% compared to placebo (95% CI, 16% to 28%). β-Blockers reduced hospitalizations due to worsening heart failure by 24% compared to placebo (95% CI, 20% to 29%). Benefits were similar for bisoprolol, metoprolol, and carvedilol regardless of NYHA class (*P* value not reported). Secondary:

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Willenheimer et al[103] CIBIS-III Bisoprolol 1.25 to 10 mg QD vs enalapril 2.5 to 10 mg BID	BE, MC, OL, PG, RCT Patients ≥65 years with stable mild to moderate CHF (NYHA II-III), LVEF of ≤35% at least 3 months prior to randomization, not on an ACE inhibitor, β-blocker or ARB therapy and no clinically relevant fluid retention of diuretic adjustment within the 7 days prior to randomization	N=1,010 1.22±0.42 years	Primary: Combined all-cause mortality or hospitalization Secondary: Combined end point at the end of the monotherapy phase and the individual components of the primary end point, cardiovascular death and cardiovascular hospitalization, permanent treatment cessation and the need for early introduction of the second drug as indicators of drug tolerability.	Primary: There were 178 patients (35.2%) with a primary end point of combined all-cause mortality or all-cause hospitalization in the bisoprolol-first group, compared to 186 (36.8%) patients in the enalapril-first group (absolute difference: –1.6%; 95% CI, –7.6 to 4.4%; HR, 0.94; 95% CI, 0.77 to 1.16; noninferiority for bisoprolol-first vs enalapril-first treatment; *P*=0.019). Secondary: The combined endpoint at the end of the monotherapy phase occurred in 109 patients in the bisoprolol-first group compared to 108 patients in the enalapril-first group (HR, 1.02; 95% CI, 0.78 to 1.33; between-group difference *P*=0.90); 23 vs 32 patients died, respectively (HR, 0.72; 95% CI, 0.42 to 1.24; between-group difference *P*=0.24); and 99 vs 92 patients had been a hospitalization, respectively (HR, 1.08; 95% CI, 0.81 to 1.43; between-group difference *P*=0.59). There were 65 deaths in the bisoprolol-first group, as compared with 73 in the enalapril-first group (HR, 0.88; 95% CI, 0.63 to 1.22; between-group difference *P*=0.44). In the bisoprolol-first group, 151 patients were hospitalized, compared to 157 patients in the enalapril-first group (HR, 0.95; 95% CI, 0.76 to 1.19; between-group difference *P*=0.66). There was not a significant difference in cardiovascular death rate observed between the bisoprolol-first (55) and enalapril-first (56) treatment groups (HR, 0.97; 95% CI, 0.67 to 1.40; between-group difference *P*=0.86). During the monotherapy phase, 35 (6.9%) patients in the bisoprolol-first group permanently discontinued therapy, compared to 49 (9.7%) patients in the enalapril-first group. During the combined-therapy phase, 19 patients (4.2%) in the bisoprolol-first group permanently discontinued bisoprolol therapy and 47 (10.4%) discontinued enalapril therapy. In the enalapril-first group, 24 patients (5.5%) permanently

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				discontinued bisoprolol and 16 (3.7%) discontinued enalapril (*P* values were not reported). There was not a statistical significant difference observed in the early introduction of the second drug between the bisoprolol-first group (39 [7.7%] patients) compared to the enalapril-first group (37 [7.3%] patients; *P*=0.81).
Di Lenarda et al[104] Metoprolol 142±44 mg QD vs carvedilol 12.5 mg to 50 mg BID	OL, PG, RCT Symptomatic (>12 months) patients with stable dilated cardiomyopathy, LVEF of ≤40% and who poorly responded to chronic treatment with metoprolol plus conventional therapy (metoprolol plus ACE inhibitor, digitalis, diuretics), persistent moderate-to-severe left ventricular dysfunction and reduced exercise tolerance	N=30 12 months	Primary: Improvement in LV function and remodeling Secondary: Effects on symptoms, QOL, exercise tolerance and ventricular arrhythmias	Primary: LVEF significantly improved in the carvedilol group (+7±3%) compared with the metoprolol group (–1±2%; *P*=0.045). LV end-systolic volume was significantly improved in the carvedilol group (–7±5) compared to the metoprolol group (+6±4 mL/m^2; *P*=0.047). There was not a significant difference in LV end-diastolic volume observed between the carvedilol (–8±7) and the metoprolol group (+7±6 mL/m^2; *P*=0.053). Secondary: There was not a significant difference observed in the NYHA class, the Heart Failure Score, the Minnesota "Living With Heart Failure" Questionnaire and submaximal exercise tolerance did not significantly change between the carvedilol and metoprolol groups. Carvedilol, compared to metoprolol, demonstrated a positive effect on ventricular ectopic beats (-12±9 vs +62±50 n/h; *P*=0.05) and couplets (–0.5±0.4 vs +1.5±0.6 n/h; *P*=0.048), but not a significant effect on episodes of nonsustained ventricular tachycardia (–0.02±0.03 vs +0.03±0.01; *P* value not reported).
Maack et al[105] Metoprolol 12.5 to 100 mg BID vs carvedilol 3.125 to 25 mg BID	OL, XO Patients with stable NYHA class I-III heart failure due to ischemic or idiopathic dilated cardiomyopathy and an LVEF of <35%	N=80 6 months	Primary: Change in LVEF and change in baseline hemodynamic properties (left ventricular end diastolic, end systolic volume,	Primary: After 6 months of treatment LVEF improved in the carvedilol group (32±3% to 36±4%; *P*<0.05 vs baseline) and in the metoprolol group (27±4% to 30±5%; *P*<0.05 vs baseline). There was not a statistical difference between the agents (*P* value not reported). There were no differences between the groups in left ventricular end diastolic, end systolic volume, NYHA functional class or any other hemodynamic parameters at rest (*P* value not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			NYHA class, etc.) Secondary: Not reported	Secondary: Not reported
Metra et al[106] Metoprolol 5 to 100 mg BID vs carvedilol 3.125 to 50 mg BID All patients continued on their usual treatment for heart failure	DB, PRO, RCT Symptomatic (≥6 months) patients with CHF caused by ischemic or nonischemic cardiomyopathy, NYHA II-IV, LVEF ≤35% and a peak VO_2 ≤25 mL/kg^{-1}/min^{-1} and on constant background therapy (furosemide and ACE inhibitor or ARB) for 1 week prior to the study	N=150 15 months	Primary: Change in LVEF Secondary: Hemodynamic variables at rest and peak exercise, maximal and submaximal exercise tolerance, QOL, NYHA functional class, and the frequency of death and urgent transplantation	Primary: Both agents significantly increased LVEF from baseline (*P*<0.001 for both) but carvedilol increased LVEF significantly greater at the than metoprolol (+10.9±11% vs +7.2±7.7%; *P*=0.038). Secondary: At the end of the study, both agents carvedilol and metoprolol increased stroke volume and stroke work indexes and decreased mean pulmonary artery pressure, pulmonary wedge pressure, and heart rate from baseline (all *P*<0.05 from baseline). However, the increase in stroke volume and stroke work indexes during exercise and the decreases in mean pulmonary artery pressure and pulmonary wedge pressure at both rest and exercise were greater with carvedilol than with metoprolol (all *P*<0.05). Carvedilol increased rest and exercise cardiac index from baseline (both *P*<0.05). Heart rate declined with both drugs at rest and exercise, but the decrease in exercise heart rate with carvedilol was greater than with metoprolol (*P*<0.05 for the difference between the groups). Both metoprolol and carvedilol significantly improved NYHA class, 6-minute walk distance, and QOL scores from baseline (all *P*<0.05), and there were no differences between the 2 treatments. Overall, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent urgent transplantation (*P* value not reported).
Poole-Wilson et al[107] COMET	DB, PG, MC, RCT Patients with NYHA II–IV heart failure,	N=3,029 58 months	Primary: All-cause mortality and the composite endpoint of	Primary: All-cause mortality was significantly lower in the carvedilol group compared to the metoprolol group (512 [34%] vs 600 [40%], respectively; HR, 0.83; 95% CI, 0.74 to 0.93; *P*=0.0017).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Carvedilol 25 mg BID vs metoprolol 50 mg BID	admission for a cardiovascular reason in the previous 2 years, an LVEF of <35%, and were stable and optimized with diuretics for ≥2 weeks and ACE inhibitor for ≥4 weeks unless not tolerated		mortality or all-cause admission Secondary: Not reported	Cardiovascular deaths were significantly lower in the carvedilol group compared to the metoprolol group (438 [29%] vs 534 [35%], respectively; HR, 0.80; 95% CI, 0.70 to 0.90; *P*=0.0004). There was not a significant difference in the composite endpoints of all-cause mortality or all-cause admission observed between the carvedilol and metoprolol groups (1,116 [74%] vs 1,160 [76%], respectively; HR, 0.94; 95% CI, 0.86 to 1.02; *P*=0.122). Secondary: Not reported
Packer, Antonopoulos et al[108] Carvedilol 50 to 100 mg/day vs metoprolol 50 to 150 mg/day or metoprolol ER 150 to 200 mg/day or placebo	MA Nineteen trials evaluating patients with NYHA class of II or III and left ventricular EF dysfunction	N=2,779 8.3 months	Primary: Change in LVEF Secondary: Not reported	Primary: In the 6 placebo-controlled trials, metoprolol significantly increased the mean LVEF by 0.063±0.002 compared to the increase with placebo of 0.025±0.001 (difference of 0.038±0.005; *P*<0.0001). In the 9 placebo-controlled trials, carvedilol significantly increased the mean LVEF by 0.079±0.001 compared to the increase with placebo of 0.012±0.001 (difference of 0.065±0.005; *P*<0.0001). Comparing the two agents, carvedilol increased the LVEF significantly greater than metoprolol (difference of 0.026±0.007; *P*=0.0002). In the 4 direct comparator trials, carvedilol significantly increased the mean LVEF by 0.089±0.002 compared to the increase with metoprolol of 0.055±0.002 (difference of 0.029±0.011; *P*=0.009). Secondary: Not reported
Arumanayagam et al[109] Carvedilol 25 mg BID vs metoprolol 50 mg BID	DB, RCT Symptomatic Chinese patients with CHF and LVEF of <45%	N=24 12 weeks	Primary: Plasma total antioxidant status, erythrocyte superoxide dismutase and glutathione peroxidase	Primary: Neither carvedilol nor metoprolol significantly reduced total antioxidant status activities after 12 weeks of therapy (1.65±0.06 to 1.68±0.09 mmol/L and 1.44±0.05 to 1.51±0.06 mmol/L, respectively; *P* values were not reported). Carvedilol significantly reduced erythrocyte superoxide dismutase activity after 12 weeks of therapy, (986±46 to 871±22 U/g Hb; *P*

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	<0.001), but metoprolol did not (790±43 to 836±46 U/g Hb; *P* value not reported). Carvedilol significantly reduced glutathione peroxidase activity after 12 weeks of therapy, (145±7 to 132±9 U/g Hb; *P* <0.05), but metoprolol did not (143±8 to 138±9 U/g Hb; *P* value not reported). Secondary: Not reported
Sanderson et al[110] Carvedilol 25 mg BID vs metoprolol 50 mg BID All patients continued on their standard therapy	DB, PG, RCT Symptomatic patients with CHF, LVEF of <45%, and on standard therapy (diuretics, digoxin and ACE inhibitor)	N=51 12 weeks	Primary: Symptom score (QOL questionnaire and NYHA class), exercise tolerance time, and LVEF Secondary: Not reported	Primary: A significant improvement in symptom scores from baseline were experienced in both the carvedilol (17.2±3 to 8.1±2; *P*<0.001) and metoprolol (13.1±1.8 to 4.8±1.4; *P*<0.001) groups, but there was not a significant difference between the agents (*P* value not reported). A significant improvement in NYHA class from baseline were experienced in both the carvedilol (2.6±0.11 to 2.2±0.12; *P*<0.001) and metoprolol (2.7±0.09 to 2.1±0.09; *P*<0.001) groups, but there was not a significant difference between the agents (*P* value not reported). A significant improvement in exercise tolerance time from baseline were experienced in both the carvedilol (1122±51 to1194±63; *P*<0.05) and metoprolol (1164±46 to 1263±52; *P*<0.01) groups, but there was not a significant difference between the agents (*P* value not reported). A significant improvement in LVEF from baseline were experienced in both the carvedilol (26±1.8 to 35±2.6; *P*<0.001) and metoprolol (25±1.8 to 31±2.5; *P*<0.001) groups, but there was not a significant difference between the agents (*P* value not reported). Secondary: Not reported
Hamaad et al[111] Carvedilol 3.125 to -25 mg BID	RCT Patients with stable LVEF of <40% and treated with diuretic and	N=31 12 weeks	Primary: blood pressure, heart rate responses and both time and frequency domain	Primary: Carvedilol significantly reduced DBP from baseline to week 12 of therapy (stage 6), but bisoprolol did not: 10±16 mm Hg (*P*=0.045) and 7±16 mm Hg, respectively (*P*=0.159), but there was not a significant difference between groups (*P* value not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs bisoprolol 1.25 to 10 mg QD	ACE inhibitor or ARB		heart rate variability Secondary: Not reported	Both carvedilol and bisoprolol significantly reduced SBP from baseline to week 12 of therapy (stage 6): 18±28 mm Hg (*P*=0.045) and 12±16 mm Hg, respectively (*P*<0.003) but there was not a significant difference between groups (*P* value not reported). Both carvedilol and bisoprolol significantly decreased mean heart rate from baseline to week 12 of therapy (stage 6): 25±20 bpm and 23±10 bpm, respectively (*P*<0.01 for both agents vs baseline) but there was not a significant difference between groups (*P*=0.708). Neither carvedilol nor bisoprolol significantly increased 4 of the 5 heart rate variability indices measured including SDNN, RMSSD, low frequency power or high frequency power (*P* values were reported). But both carvedilol and bisoprolol significantly increased TI from baseline to week 12 of therapy (stage 6): 7±6 (*P*<0.01) and 5±6 (*P*=0.01), respectively, but there was not a significant difference between groups (*P* value not reported). Secondary: Not reported
Arrhythmia				
Kettering et al[112] Metoprolol 25 to 200 mg/day vs sotalol 40 to 480 mg/day	PRO, RCT Symptomatic patients between 18 and 80 years with sustained ventricular tachycardia and/or ventricular fibrillation requiring an implantable cardioverter defibrillator	N=100 2 years	Primary: ventricular tachycardia/ ventricular fibrillation recurrence requiring implantable cardioverter defibrillator intervention Secondary: Total mortality	Primary: There was not a significant difference in ventricular tachycardia/ ventricular fibrillation recurrence rates observed between the metoprolol group (33 patients) and the sotalol group (30 patients; *P*=0.68). After 1 year of treatment, 46.3% of patients in the metoprolol group and 54.7% of patients in the sotalol group were free of a recurrence of ventricular tachycardia or ventricular fibrillation (*P*=0.68). After 2 years, rates were 31.5% and 36.6%, respectively (*P* value not reported). Secondary: There was not a significant difference in mortality rates observed between the metoprolol group (8 deaths) and the sotalol group (6

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients; *P*=0.43).
Seidl et al[113] Metoprolol 50 mg/day vs sotalol 80 mg/day The doses of the study medications were titrated to the maximum titrates dose.	OL, RCT Patients >18 years of age requiring treatment if life-threatening ventricular tachycardia/ ventricular fibrillation who required an implantable cardioverter defibrillator due to noninducible or drug refractory (≥1 unsuccessful antiarrhythmic trial) arrhythmias	N=70 26±16 months	Primary: Recurrence of ventricular tachycardia requiring antitachycardia pacing, fast ventricular tachycardia or ventricular fibrillation requiring implantable cardioverter defibrillator, discharges, and total mortality Secondary: Not reported	Primary: Actuarial rates for absence of ventricular tachycardia recurrence were significantly higher in the metoprolol group vs the sotalol group at 1 and 2 years (83% and 80% vs 57% and 51%, respectively; *P*=0.016). Actuarial rates for absence of recurrence of a fast ventricular tachycardia or ventricular fibrillation were significantly higher in the metoprolol group vs the sotalol group 1 and 2 years (88% and 80% vs 54% and 46%, respectively; *P*=0.002) Actuarial survival rates at 1 and 2 years were not significantly different between the metoprolol and sotalol groups (94% and 91% vs 86% and 83%, respectively; *P*=0.287) Secondary: Not reported
Steeds et al[114] Sotalol 80 mg BID vs atenolol 50 mg QD	OL, PRO, RCT, XO Symptomatic patients over 50 years of age with paroxysmal atrial fibrillation documented on electrocardiogram	N=47 2 months	Primary: Frequency of paroxysmal atrial fibrillation Secondary: Average and total duration of paroxysmal atrial fibrillation, total ectopic count and symptom assessments	Primary: There was not a significant difference in frequency of episodes of paroxysmal atrial fibrillation observed between the sotalol and atenolol groups (median difference 0 min, 95% CI, 0 to 1; *P*=0.47). Secondary: There was not a significant difference in average duration of episodes of paroxysmal atrial fibrillation observed between the sotalol and atenolol groups (median difference, 0 min; 95% CI, 0 to 1 min; *P*=0.31) or in total duration of episodes of paroxysmal atrial fibrillation (median difference, 0 min; 95% CI, −1 to 2 min; *P*=0.51). There was not a significant difference in total ectopic count observed between the sotalol and atenolol groups (median difference, –123; 95% CI, −362 to 135; *P*=0.14) during either treatment period. There was not a significant difference in tolerance and symptom

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				scores observed between the sotalol and atenolol groups (median difference, –5; 95% CI, −20 to 5; *P*=0.26) Secondary: Not reported
Balcetyte-Harris et al[115] Esmolol 0.5 mg/kg over 5 minutes then 0.05 mg/kg/min titrated to heart rate of 55 to 65 bpm and SBP >100 mm Hg for up to 24 hours vs oral β-blocker (metoprolol ≥50 mg/day was the preferred agent)	OL, RCT Patients referred for elective CABG without concomitant valve replacement who were in sinus rhythm	N=50 72 hours	Primary: Development of atrial fibrillation lasting >30 mins Secondary: Development of adverse events, hypotension (SBP <90 mm Hg), symptomatic bradycardia or CHF (LV failure)	Primary: There was not a significant difference in development of atrial fibrillation after CABG between the esmolol and β-blocker group (7 [26%] patients' vs 6 [26%] patients, respectively; *P* values not reported). Secondary: Significantly more patients in the esmolol group experienced significant adverse events compared to the patients in the β-blocker group (11 [41%] vs 1 [4%] patients, respectively; *P*=0.006). Significantly more patients in the esmolol group experienced hypotension compared to the patients in the β-blocker group (8 vs 1 patient, respectively; *P*=0.03). There was not a statistically significant difference between the esmolol and the β-blocker group in the development bradycardia requiring pacing (2 vs 0 patients, respectively; *P* values was not reported) and in LV failure (1 vs 0 patients, respectively; *P* values not reported).
Lee et al[116] Amiodarone vs sotalol vs β-blockers (agents not specified)	RETRO Patients with atrial fibrillation and/or CHF (NYHA class ≥III) and an implantable cardioverter defibrillator	N=55 2.6±2 years	Primary: Cumulative rates of inappropriate shocks Secondary: Not reported	Primary: Amiodarone demonstrated a significantly lower rate of inappropriate shock was compared β-blocker group (27.3% vs 70.6% at 4 years; *P*=0.003). This demonstrated an 83% reduction compared to the β-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 4 years; *P*=0.29). There was not a significant difference in rates of inappropriate shocks observed between the sotalol and β-blocker groups (54.3% vs 70.6% at 4 years; *P*=0.16).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Doses of the agents were not specified				Secondary: Not reported
Connolly et al[117] OPTIC β-Blocker (bisoprolol, carvedilol or metoprolol) vs sotalol 240 mg/day in two to three divided doses vs amiodarone 200 mg QD 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	DB, MC, RCT Patients who received an implantable cardioverter defibrillator within 21 days of randomization, had sustained ventricular tachycardia, ventricular fibrillation or cardiac arrest (not ≤72 hours of acute myocardial infarction), 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	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 β-blocker group, 26 (24.3%) in the sotalol group, and 12 (10.3%) in the amiodarone plus β-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 β-blocker group significantly reduced the risk of shock compared with β-blocker alone (HR, 0.27; 95% CI, 0.14 to 0.52; *P*<.001) and sotalol (HR, 0.43; 95% CI, 0.22 to 0.85; *P*=.02). Sotalol did not significantly reduce the risk of shock compared to the β-blocker alone group (HR, 0.61; 95% CI, 0.37 to 1.01; *P*=0.055). Secondary: Not reported
Angina				
Weiss et al[118] Carvedilol 12.5 to 50 mg BID vs placebo	DB, MC, XO Patients with 2 stress tests which evoked the following within 3 to 8 minutes: anginal pain of the intensity at which a patient would usually stop activity and/or take a	N=122 12 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: The carvedilol 25 mg and 50 mg groups significantly reduced the time to angina compared to placebo (25 mg: 337 s, *P*=0.0039; 50 mg: 345 s; *P*<0.001 vs 316 s). The carvedilol 25 mg and 50 mg groups significantly reduced the time to 1-mm ST-segment depression compared to placebo (25 mg: 313 s; 50 mg: 323 s vs 301 s [*P*<0.0001 for both]).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	nitroglycerin tablet and ischemic changes of ≥1 mm of ST-segment depression and the total exercise time measured on the second qualifying exercise treadmill test could not differ from the first trough exercise treadmill test by .20%, and for time to angina and time to 1-mm ST-segment depression, the difference between visits could not be 90 seconds.			The percentage of patients reporting any adverse experience was slightly less in those receiving placebo (placebo: 28.4%; 12.5 mg: 33.1%; 25 mg: 34.5%; 50 mg: 31.9%; *P* values not reported). Adverse events included dizziness, fatigue, headache, dyspepsia and any hypotensive event. The clinical significance of the adverse events was not reported. Secondary: Not reported
Hauf-Zachariou et al[119] Carvedilol 25 mg BID vs verapamil 120 mg TID	DB, MC, PG, RCT Patients 18-75 years with a confirmed diagnosis of coronary artery disease, exertional chest pain relieved by rest or glyceryl trinitrate for ≥2 months and 2 exercise tests during the placebo run-in phase with angina and ≥1 mm ST-segment depression, 60 ms after J-point, within 3±9 min of the beginning of the test and the two tests could not differ by more than 15% with regard to total exercise time	N=313 12 weeks	Primary: Total exercise time, time to onset of angina, and time to 1 mm ST-segment depression, blood pressure, heart rate and rate pressure product Secondary: Not reported	Primary: There was not a significant difference in total exercise time observed between the carvedilol (increased from 378 s to 436 s) and verapamil (increased from 386 s to 438 s) groups (RR, 1.14; 90% CI, 0.85±1.52; *P* value not reported). There was not a significant difference observed between the carvedilol and verapamil groups in time to onset of angina (increase from 296 s to 325 s vs 285 s to 326 s) and in time to 1 mm ST-segment depression (increase from 267 s to 298 s vs 286 s to 302 s); *P* values not reported. At peak exercise and at maximum comparable workload, carvedilol significantly reduced SBP (from 175 to 166 mm Hg) compared to verapamil (from 173 to 173 mm Hg); *P* value not reported). At peak exercise and at maximum comparable workload, carvedilol significantly reduced heart rate (from 123 to 112 mm Hg) compared to verapamil (from 124 to 120 mm Hg); *P* value not reported). At peak exercise and at maximum comparable workload, carvedilol significantly reduced rate pressure product (from 21564 to 18802 mm Hg) compared to verapamil (from 21488 to 20992 mm Hg); *P* value

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not reported). Secondary: Not reported
van der Does et al[120] Carvedilol 25 to 50 mg BID vs metoprolol 50 to 100 mg BID	DB, MC, RCT Male or female (postmenopausal or using reliable contraceptive methods) patients ≤80 years of age with CHD and chronic angina pectoris stable for at least the preceding 2 months, exertional angina with symptoms improving after taking short acting nitrates or after a period of rest, and 1 exercise test performed that was limited by moderate anginal pain	N=368 3 months	Primary: Moderate anginal pain and time to ST-1-mm segment depression Secondary: Not reported	Primary: Compared to baseline, both carvedilol and metoprolol significantly decreased time to anginal pain during exercise test (+77s [+20 to +140] and +76 [+25 to +155], respectively; *P*<0.001 for both). Compared to baseline, both carvedilol and metoprolol significantly decreased time to ST- 1-mm segment depression during exercise test (+75.5 s [+47 to +154 s] and +60 [0 to +146 s], respectively; *P*<0.001 for both). Carvedilol significantly improved the time to 1-mm ST-segment depression compared to metoprolol (RR, 1.386; 95% CI, 1.045 to 1.839; *P*<0.05) Secondary: Not reported
Kardas P[121] Betaxolol 20 mg QD vs metoprolol 50 mg BID	OL, PG, RCT Patients 40-75 years with ischemic heart disease NYHA class I-II, no prior β-blocker treatment and whose mental state enabled conscious participation in the study	N=112 8 weeks	Primary: Overall compliance Secondary: Drug effectiveness and health-related QOL	Primary: The overall compliance significantly higher in the betaxolol group compared to the metoprolol group (86.5±21.3% vs 76.1±26.3%, respectively; *P*=0.002). Secondary: There was not a significant difference in chest pain episodes observed between the betaxolol and metoprolol groups compared from baseline (0.42/week and 0.46/week change in episodes, respectively; *P*>0.05). Overall, QOL dimensions measured (i.e., general well-being, sleep, mood, etc) were similar among both treatment groups, with the exception of physical function in which a significantly greater improvement was observed in the betaxolol group compared to the metoprolol group (42.9 vs 15.2 patients improved, respectively;

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.01).
Pandhi et al[122] Acebutolol 100 to 400 mg TID vs propranolol 40 to 160 mg TID vs placebo	DB, XO Patients with classical anginal symptoms of effort with at least 7 attacks per week and angina being stable for at least 8-12 weeks	N=24 18 weeks	Primary: Incidence of anginal attack, number of nitroglycerin tablets used, exercise tolerance and side effects Secondary: Not reported	Primary: Both acebutolol and propranolol significantly reduced the incidence of anginal attacks per week compared to placebo (*P*<0.001 for both groups), but the difference between the 2 groups was not significant (*P*>0.05). Both acebutolol and propranolol significantly reduced the number of nitroglycerin tablets used per week compared to placebo (*P*<0.001 for both groups), but the difference between the 2 groups was not significant (*P*>0.05). Both acebutolol and propranolol significantly improved exercise tolerance compared to placebo (*P*<0.001), but the difference between the 2 groups was not significant (*P*>0.05). Side effects reported (i.e., insomnia, sweating, bitter taste, heart burn, and muscle weakness) were similar between the two treatment groups (*P* values were not reported). Clinical significance of the side effects was not reported. Secondary: Not reported
Savanitto et al[123] <u>Weeks 1-6</u>: Metoprolol ER 200 mg QD vs nifedipine 20 mg BID <u>Weeks 7-10</u>: Metoprolol ER 200 mg QD plus placebo vs	DB, MC, RCT Patients with typical angina1 symptoms that had been stable for ~6 months, who showed a positive response to exercise stress testing with 23 min of exercise tolerance and were in sinus rhythm and had an analyzable ST segment on electrocardiography	N=280 6 weeks	Primary: Angina frequency, exercise tolerance, and safety Secondary: Not reported	Primary: At week 6, both metoprolol (mean change, –1.95; 95 % CI, –1.25 to –2.64) and nifedipine (mean change, –1.57; 95 % CI, –0.69 to –2.45) significantly reduced the frequency of angina compared to baseline, but there was not a statistical difference between groups. At the end of 10 weeks, there was not a statistical difference observed between the groups. At week 6, both metoprolol and nifedipine significantly increased the mean exercise time to l-mm ST-segment depression compared to baseline (both *P*<0.01); but metoprolol was significantly more effective than nifedipine (*P*<0.05). At week 10, the groups randomized to combination therapy had a

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metoprolol ER 200 mg QD and nifedipine 20 mg BID vs nifedipine 20 mg BID plus placebo				further increase in time to l-mm ST-segment depression (*P*<0.05 vs placebo). There were 14 cardiovascular events including 1 sudden death, 3 acute myocardial infarctions, 8 cases of unstable angina, 1 of syncope and 1 of stroke and the incidence of these events did not differ among the treatment groups (*P* values were not reported). Secondary: Not reported
Post Myocardial Infarction Maintenance Therapy				
Olsson et al[124] Metoprolol 100 mg BID vs placebo	MA Five double-blind, placebo-controlled, randomized trials evaluating effects of mortality post MI	N=5,474 3 months to 3 years	Primary: All-cause mortality and sudden deaths Secondary: Not reported	Primary: Metoprolol significantly reduced all-cause mortality compared to placebo (188 vs 223 deaths; *P*=0.036). Metoprolol significantly reduced sudden deaths compared to placebo (62 vs 104 deaths; *P*=0.002). Secondary: Not reported
Jonsson et al[125] Carvedilol 6.25 to 25 mg BID vs atenolol 12.5 to 50 mg BID	BE, OL, RCT Patients between 18 to 80 years of age with chest pain consistent with an acute myocardial infarction, admitted to the hospital 24 hours after onset and a confirmed diagnosis with significant increase in cardiac enzymes	N=232 1.5±1.3 years	Primary: Change in global or regional LVEF after 12 months, cardiovascular endpoints and adverse events Secondary: Not reported	Primary: At baseline, mean global LVEF was 54.8% in the carvedilol and 53.0% in the atenolol group and increased after 12 months to 57.1% in the carvedilol and 56.0% in the atenolol group. There was not a significant difference between treatment groups for change in global or regional LVEF (values were not reported), (*P* value not reported). There was not a significant difference in the rates of occurrence of the first serious cardiovascular events observed between the carvedilol and atenolol groups after adjustment for diuretic use (0.247 vs 0.299; RR, 0.83; 95% CI, 0.56 to 1.23; *P*=0.39). Of the nonserious adverse events reported, a greater incidence of colds hand and feet were reported in the atenolol group (38 [33.3%]) compared to the carvedilol group (24 [20%]; *P*=0.025). Secondary:

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Gottlieb et al[126] Atenolol vs metoprolol vs propranolol vs other (not specified) Doses for the agents were not specified.	RETRO Patients discharged from the hospital with the diagnosis of an acute myocardial infarction and on a β-blocker	N=69,338 2 years	Primary: Mortality rates at one year and two years Secondary: Not reported	Primary: β-Blockers demonstrated an 40% overall reduction in mortality compared to those patient who did not receive β-blocker therapy (*P* values not reported). One year mortality rates in the three groups were metoprolol 8.32% (CI, 8.07 to 8.58, atenolol 8.16% (CI, 7.76 to 8.58), propranolol 9.55% (CI, 9.69 to 10.48), and other 9.19% (CI, 8.16 to 10.33), (*P* values not reported). Two-year mortality rates in the three groups were metoprolol 13.52% (CI, 13.21 to 13.84), atenolol 13.41% (CI, 12.91 to 13.93), propranolol 15.91% (CI, 14.83 to 17.05), and other 15.17% (CI, 13.88 to 16.56). There were no differences between atenolol and metoprolol at the end of the 2 years, both of which were statistically better than propranolol (*P* values not reported). Compared with metoprolol, patients discharged on propranolol had 15% increased mortality at 1 year and an 18% increased mortality at 2 years, which were significantly higher than metoprolol (*P* values not reported). Secondary: Not reported
Freemantle et al[127] β-blockers (acebutolol, alprenolol, atenolol, betaxolol, carvedilol, labetalol, oxprenolol, pindolol, practolol, propranolol, sotalol, timolol and xamoterol) vs	MA Eighty-two randomized controlled trials evaluating patients with acute or past myocardial infarction	N=54,234 6-48 months	Primary: All-cause mortality Secondary: Nonfatal reinfarction and withdrawal from treatment	Primary: The pooled random effects in short term trials demonstrated a mortality rate of 10.5% (3,062 out of 29,260 patients) which is a 4% reduction compared to the controlled groups (OR, 0.96; 95% CI, 0.85 to 1.08; *P* value not reported). The pooled random effects in long term trials demonstrated a mortality rate of 9.7% (2415 out of 24974 patients) which is 23% reduction when compared to the controlled groups (OR, 0.77;95% CI, 0.69 to 0.85; *P* values was not reported). Individually, only four drugs achieved a statistically significant

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
control (agents were not specified)				reduction in the death: propranolol (OR, 0.71; CI, 0.59 to 0.85]), timolol (OR, 0.59; CI, 0.46 to 0.77), metoprolol (OR, 0.80; CI, 0.66 to 0.96; and acebutolol (OR, 0.49; CI, 0.25 to 0.93); *P* values not reported. Secondary: A reduction in nonfatal reinfarctions of 0.9 events in every 100 (0.3 to 1.6) annually is suggested by this analysis; therefore about 107 patients would require treatment for 1 year to avoid one nonfatal reinfarction. Overall, 5,151 of 21,954 patients (23.5%) withdrew from treatment. with withdrawal occurring more often in the β-blocker groups. When comparing to placebo, the difference in annualized rate of withdrawal was 1.16 in 100 patients treated (1.16; 95% CI, 0.56 to 1.76); *P* value was not reported).
Migraine Prophylaxis				
Schellenburg et al[128] Metoprolol 47.5 to 142.5 mg vs nebivolol 5 mg	DB, PRO, RCT Patients 18-65 years with the diagnosis of migraine with/without aura, a ≥1 year history, onset prior to 50 years of age, written record of attacks for the previous 3 months, and a ≥2 attacks per month during screening	N=38 30 weeks	Primary: Number of migraine attacks Secondary: Onset of action, duration of attacks, responder rate, severity, use of pain medication, migraine disability assessment and QOL score	Primary: There was not a significant difference in the frequency of migraine attacks observed between the metoprolol and nebivolol groups (1.3±1.0 vs 1.6±1.5, respectively; *P* value not reported). Secondary: There was not a significant difference in any of the secondary endpoint measurements observed between the metoprolol and nebivolol groups (*P* values not reported). Use of acute pain medication decreased on both drugs, as well as accompanying symptoms. Both patients' and physicians' evaluations of disability and disease status were similarly favorable to the 2 treatments (*P* values not reported).
Rao et al[129] Propranolol 40 mg BID vs	MC Patients with ≥2 migraine attacks per week	N=259 3 months	Primary: Response to therapy scores for frequency, severity and duration of attacks	Primary: Propranolol, cyproheptadine and cyproheptadine plus propranolol significantly reduced the frequency of migraine attacks compared to placebo based on response to therapy scores (2.85±0.2, 3.12±0.1 and 1.77±0.44, respectively; *P*<0.05 for all groups compared to placebo) but the cyproheptadine plus propranolol group was significantly better

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cyproheptadine 2mg BID vs cyproheptadine 2mg BID plus propranolol 40 mg BID vs placebo			Secondary: Not reported	when compared to propranolol alone (*P*<0.05). Propranolol, cyproheptadine and cyproheptadine plus propranolol significantly reduced the duration of migraine attacks compared to placebo based on response to therapy scores (2.83±0.2, 3.09±0.19 and 1.77±0.44, respectively; *P*<0.05 for all groups compared to placebo) but the cyproheptadine and the cyproheptadine plus propranolol groups were significantly better when compared to propranolol alone (*P*<0.05). Propranolol, cyproheptadine and cyproheptadine plus propranolol significantly reduced the severity of migraine attacks compared to placebo based on response to therapy scores (2.87±0.13, 3.10±0.19 and 1.64±0.45, respectively; *P*<0.05 for all groups compared to placebo) but the cyproheptadine and the cyproheptadine plus propranolol groups were significantly better when compared to propranolol alone (*P*<0.05). Secondary: Not reported
Linde et al[130] Propranolol 60 to 320 mg/day vs placebo or another agent (CCBs, other β-blockers, or other agent)	MA Twenty six randomized and quasi-randomized clinical trials of at least 4 weeks duration comparing clinical effects of propranolol with placebo or another drug in adult migraine sufferers	N=5,072 4-30 weeks	Primary: Headache and migraine frequency Secondary: Not reported	Primary: Compared to placebo, propranolol showed a statistical advantage in response to treatment with overall relative risk of response ("responder ratio") of 1.94 (95% CI, 1.61 to 2.35; *P* value not reported). Compared to placebo, propranolol showed a statistical advantage for the reduction of frequency of migraines with overall mean difference of –0.40 (95% CI, –0.56 to –0.24; *P* values not reported). Propranolol did not demonstrate a significantly greater response to treatment compared to CCBs with an overall responder ratio of 1.00 (95% CI, 0.92 to 1.09; *P* values not reported). Propranolol did not demonstrate a significantly greater reduction in migraine frequency compared to CCBs with an overall mean difference of –0.02 (95% CI, 0.12 to 0.08; *P* values not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In the three trials comparing propranolol and nadolol, the overall responder ratio favored nadolol over propranolol (responder ratio 0.60; 95% CI, 0.37 to 0.97), but the results of the three trials were contradictory. In the three trials comparing propranolol and metoprolol, there was not a significant difference observed in the overall responder ratio between the two groups (responder ratio, 0.78; 95% CI, 0.56 to 1.09). Propranolol did not demonstrate a significantly greater reduction in migraine frequency compared to the other β-blockers with an overall mean difference of –0.01 (95% CI, 0.24 to 0.22; *P* values not reported). A quantitative metaanalyses was not performed on studies comparing propranolol to other drugs due to the great variety of comparator drugs used. One trial was significantly in favor of propranolol (vs amitriptyline), five with a trend in favor of propranolol, 11 showing no difference, two with a trend in favor of the comparator drug, and one not interpretable; one of the two comparisons of propranolol alone and propranolol in combination with amitriptyline was classified as no difference, and the other as showing a trend in favor of the combination (*P* values not reported). Secondary: Not reported
Essential Tremor				
Calzetti et al[131] Metoprolol 150 mg/dose vs propranolol 120 mg/dose vs	DB, PC, RCT Patients 19-72 years with essential tremor and symptomatic for ≥1 year prior to the study	N=23 3 weeks	Primary: Tremor magnitude, heart rate and blood pressure Secondary: Not reported	Primary: Both metoprolol (47±9.7%) and propranolol (55±5.0%) significantly decreased tremor magnitude from baseline compared to placebo (22±7.3%; *P*<0.01 for both treatments compared to placebo), but there was not a significant difference observed between the metoprolol and propranolol groups (*P* value not reported). Both propranolol (0.073) and metoprolol (0.01) significantly diminished the normal increase in pulse rate on standing (*P*<0.01) and placebo had no effect on such pulse rate (*P* value not reported). There

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				was not a significant difference observed between the metoprolol and propranolol groups (*P* value not reported). Both metoprolol and propranolol significantly reduced the SBP from baseline compared to placebo, in the supine and standing positions (*P*<0.05). Secondary: Not reported
Yetimalar et al[132] Propranolol 120 mg/day vs olanzapine 20 mg/day	DB, RCT, XO Patients with essential tremor and previous therapy with ≥1 medications for essential tremor (acetazolamide, clonazepam, diazepam gabapentin, primidone, propranolol) without significant benefit which was withdrawn ≥1 month before study medication was given	N=38 74 days	Primary: Tremor and global QOL Secondary: Not reported	Primary: After 30 days, both propranolol and olanzapine significantly reduced the all tremor evaluation measures (i.e., speaking, eating, dressing, writing working, etc) compared to baseline (*P*=0.000), but at the end of the study, olanzapine significantly improved all tremor evaluation measures (*P*<0.05) except hygiene (*P* =0.08) as compared to propranolol. Both propranolol (63%) and olanzapine (87%) significantly improved global QOL from baseline (*P* values were not reported), but olanzapine significantly improved the global QOL score compared to propranolol (4.5±0.7 vs 3.6±0.9; *P*=0.000). Secondary: Not reported
Gironell et al[133] Propranolol 40 mg TID vs gabapentin 400 mg TID vs placebo	DB, PC, XO Patients with moderate to severe essential tremor that was chronic (≥5 years), persistent, and bilateral postural tremor with or without kinetic tremor involving hands or forearms, with no other neurological abnormalities or explanation for tremor	N=16 66 days	Primary: Tremor Clinical Rating Scale, accelerometric recordings, self-reported disability scale Secondary: Not reported	Primary: Both gabapentin and propranolol significantly reduced the clinical examination and motor task performance components of the Tremor Clinical Rating Scale compared to placebo (−3.10±1.10; *P*=0.01 and −4.50±1.10; *P*=0.001, respectively), and significant differences were not observed between the gabapentin and propranolol groups (1.40±1.16; *P*=0.23). Both gabapentin and propranolol significantly reduced the activities of daily living component of the Tremor Clinical Rating Scale compared to placebo (−3.03±1.46; *P*<0.05 and −4.95±1.46; *P*=0.002, respectively), and significant differences were not observed between the gabapentin and propranolol groups (1.92±1.46; *P*=0.20).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both gabapentin and propranolol significantly reduced the patient's subjective assessment of the Tremor Clinical Rating Scale compared to placebo (1.37±0.46; *P*=0.006 and 1.44±0.46; *P*=0.004, respectively). Significant differences were not observed between the gabapentin and the propranolol groups (−0.07±0.46; *P*=0.89). Both gabapentin and propranolol significantly reduced the absolute power of the dominant frequency peak of accelerometry compared to placebo (–2352.0±1153.3; *P*=0.05 and -2282.14±1116.58; *P*=0.05, respectively), but significant differences were not observed between the gabapentin and the propranolol groups (−70.39±1165.22; *P*=0.95. Gabapentin significantly reduced the self-reported disability scale score more than placebo (−6.04±2.75; *P*=0.04) and propranolol did not (−4.48±2.75; *P*=0.11), but there were no significant differences between the gabapentin and propranolol groups (−1.55±2.75; *P*=0.58).

Drug regimen abbreviations: BID=twice daily, COER=controlled onset extended-release, CR=controlled release, ER=extended release, QD=daily, TID=three times daily, XL=extended release
Study abbreviations: BE=blinded endpoint, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta analysis, MC=multicenter, OL=open-label, PC=placebo-controlled , PG=parallel group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, RR=relative risk, RMSSD=root mean square of successive RR intervals, SDNN=standard deviation of the normal RR intervals, SEM=standard error of the mean, SB=single-blinded, XO=cross-over
ACE=angiotensin converting enzyme, AIx=augmentation index, aPWV=aortic pulse wave velocity, ARB=angiotensin receptor blocker, β-blockers=β-adrenergic blocking agents, bpm=beats per minute, CABG=coronary artery bypass graft, CCBs=calcium channel blocking agents, CHD=coronary heart disease, CHF=congestive/chronic heart failure, DBP=diastolic blood pressure, ET=essential tremor, HCTZ=hydrochlorothiazide, HbA_{1c}=hemoglobin, LV=left ventricular, LVEF=left ventricular ejection fraction, NIDDM=noninsulin dependent diabetes mellitus, NYHA=New York Heart Association, pro-BNP= pro-B-type natriuretic peptide, QOL=quality of life, RAS=renin-angiotensin system, SBP=systolic blood pressure, TI=triangular index, WHO=World Health Organization

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity β-Adrenergic Blocking Agents

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
acebutolol	capsule	Sectral®*	$$$	$
atenolol	injection, tablet	Tenormin®*	$$$	$
betaxolol	tablet	Kerlone®*	$$	$
bisoprolol	tablet	Zebeta®*	$$-$$$	$-$$
carvedilol	extended-release capsule, tablet	Coreg®*, Coreg CR®	$$$-$$$$	$
labetalol	injection, tablet	Normodyne®*, Trandate®*	$$-$$$$	$
metoprolol succinate	extended-release tablet	Toprol XL®*	$$	$$
metoprolol tartrate	injection, tablet	Lopressor®*	$	$
nadolol	tablet	Corgard®*	$$$	$
nebivolol	tablet	Bystolic®	$$	N/A
penbutolol	tablet	Levatol®	$$$	N/A
pindolol	tablet	Visken®*†	N/A	$
propranolol	injection, solution, extended-release capsule, long-acting capsule, tablet	Inderal®*, Inderal LA®*, InnoPran XL®*	$$$-$$$$	$

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
sotalol	tablet	Betapace®*, Betapace AF®*	$$$$	$$$
timolol	tablet	Blocadren®*†	N/A	$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

β-adrenergic blocking agents (β-blockers) are a related group of drugs that block the effects of catecholamines on β receptors. β-Blockers have a range of Food and Drug Administration (FDA)-approved indications as they differ in pharmacokinetic properties such as adrenergic-receptor blocking activity, membrane stabilizing activity, intrinsic sympathomimetic activities and lipophilicity.[1-42] Propranolol is the most lipophilic agent within the class which allows the drug to cross the blood-brain barrier and penetrate the central nervous system (CNS).[2,17,34-36] Due to this distinct property, propranolol has additional FDA indications not seen with the other agents, including migraine prophylaxis and essential tremor, but penetration into the CNS can also increase the potential for side effects such as dizziness and drowsiness.[2,17,35]

One of the most common uses for β-blockers is for the management of hypertension. Although the exact mechanism is unknown, when administered at effective doses, β-blockers cause clinically relevant blood pressure reductions in hypertensive patients.[2,73,80-83, 85] In addition, several studies have demonstrated a significant reduction in blood pressure with these agents, but no major differences have been found among agents.[73,80-83,85] The current National Heart, Lung, and Blood Institute (NHLBI): The Seventh Report Of The Joint National Committee (JNC-7) guidelines recommend β-blocker therapy for patients with hypertension and stable angina or post-myocardial infarction (MI).[54]

The American College of Cardiology (ACC)/American Heart Association (AHA) 2005 CHF guidelines recommend β-blockers for the management of heart failure.[48] The guideline recommends β-blockers (bisoprolol, carvedilol, or extended-release metoprolol) in all stable patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated.[48] Bisoprolol, carvedilol and sustained-release metoprolol have been proven to reduce mortality in clinical trials.[94-97,99104] Carvedilol and sustained-release metoprolol are the only β-blockers with an FDA-approved indication for the treatment of heart failure. Several studies have demonstrated the benefits of these two agents for heart failure; however, studies comparing them have failed to show any consistent differences in efficacy between the two.[104-107,110] One meta-analysis that evaluated the results of 4 comparator studies reported that carvedilol significantly improved the mean left ventricular ejection fraction over metoprolol.[108]

The ACC/AHA 2007 ST-Elevation Myocardial Infarction guidelines recommend β-blocker therapy for all patients.[47] When treating patients post-MI with β-blockers, one agent in this class is not recommended over another as the benefits are assumed to be a class effect.[125-127,134-137]

When using β-blockers for the prophylaxis of migraine, the guidelines recommend propranolol or timolol.[66,138-139] Clinical trials have demonstrated significant reductions in migraine frequency and severity with the use of propranolol and other β-blockers.[128-130]

In general, the side-effect profiles of the β-blockers are similar. Some of the main side effects common to the drugs in this class include fatigue, cold hands, dizziness and weakness.[6-10,12-25,27-42] β-Blockers that are more selective for the β_1-receptors (in the heart) such as atenolol and metoprolol may be safer to use in those with bronchospastic diseases as these are less likely to cause severe adverse effects including bronchospasm and vasoconstriction.[2] Contraindications to the β-blockers include sinus bradycardia, second and third degree heart block, and cardiogenic shock.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity β-adrenergic blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of β-Adrenergic Blocking Agents
Combination Products
AHFS Class 242400
September 10, 2008

I. Overview

This review of the combination β-adrenergic blocking agents covers 6 products which are approved by the Food and Drug Administration (FDA) for hypertension. Each of these combination products contains a β-adrenergic blocking agent (β-blocker) and a thiazide-type diuretic.[1-6] The individual components have different mechanisms and sites of action. The antihypertensive mechanism of action of the β-blockers has not been established; however, many mechanisms have been proposed. They include competitive antagonism of catecholamines at peripheral adrenergic sites, resulting in a reduction of cardiac output and inhibition of renin release from the kidney, and a central nervous system action leading to a reduction in sympathetic outflow to the periphery.[1-7]

The other components of β-adrenergic blocking agents combination products are thiazide diuretics, including hydrochlorothiazide and bendroflumethiazide, and chlorthalidone, a "thiazide-like" diuretic which is structurally unrelated to thiazides but shares their mechanism of action.[8-9] All thiazide-type diuretics increase the excretion of sodium and chloride by inhibition of the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules.[10] When combined with a β-blocker they produce an additive antihypertensive effect because the decrease in sodium excretion from the β-blocker is reversed by the diuretic. In addition, stimulation of renin release by the kidneys from the diuretic is suppressed by the β-blocker, and diuretic-induced hypokalemia is modified.[11-12]

There are pharmacologic and pharmacokinetic differences between the various β-blockers included in the combination products; however, the primary impact of these differences is upon drug metabolism and side effect profiles, not upon efficacy.[13] There are at least 3 distinct types of β receptors distributed throughout the body, β_1, β_2, and β_3 receptors.[7] β_1 receptors are located predominantly in the heart and kidney. Agents that have a greater affinity to β_1 receptors are considered to be cardioselective. Cardioselective agents may be safer in patients with asthma, chronic obstructive pulmonary disease and peripheral vascular disease because they have less inhibition of the β_2 receptors, which mediate vasoconstriction and bronchospasm.[14] Cardioselectivity is dose dependent; therefore, β_2 blockade can occur at higher doses with these agents.[7] The β-blockers that are included within this review can also be arranged by their relative lipophilicity, with some being lipophilic (metoprolol and propranolol) and others being considered hydrophilic (atenolol, bisoprolol, nadolol, and timolol).[1-6]

The combination β-adrenergic blocking agents that are included in this review are listed in Table 1. As noted in the table, there are many generic formulations for the combination β-adrenergic blocking agents. This review encompasses all dosage forms and strengths.

Table 1. Combination β-Adrenergic Blocking Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
atenolol and chlorthalidone	tablet	Tenoretic®*	atenolol and chlorthalidone
bisoprolol and hydrochlorothiazide	tablet	Ziac®*	bisoprolol and hydrochlorothiazide
metoprolol and hydrochlorothiazide	tablet	Lopressor HCT®*	metoprolol and hydrochlorothiazide
nadolol and bendroflumethiazide	tablet	Corzide®*	nadolol and bendroflumethiazide
propranolol and hydrochlorothiazide	tablet	Inderide®*	propranolol and hydrochlorothiazide

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
timolol and hydrochlorothiazide	tablet	Timolide®	none

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

The cardioselectivity of the β-blockers used in fixed-dose combination products is highlighted in Table 2.

Table 2. Selected Pharmacologic Properties of β-Adrenergic Blocking Agents Used in Combination Products [1-7,15,16]

Drug	Adrenergic-Receptor Blocking Activity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity
Atenolol	β_1*	0	0
Bisoprolol	β_1*	0	0
Metoprolol	β_1*	0†	0
Nadolol	β_1 - β_2	0	0
Propranolol	β_1 - β_2	++	0
Timolol	β_1 - β_2	0	0

0=none; +=low; ++=moderate; +++=high
*Inhibits β_2 receptors (bronchial and vascular) at higher doses.
†Detectable only at doses much greater than required for β blockade.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines using the combination β-adrenergic blocking agents (β-blockers) are listed in Table 3. Most guidelines recommend diuretics as first-line therapy for patients with uncomplicated hypertension. Patients may need more than one antihypertensive agent to reach target blood pressure. The add-on agent that is chosen may be influenced by factors such as the patient's cardiovascular risk profile, co-morbid illnesses and the drug's side effect profile. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), compelling comorbidities for the selection of a β-blocker for initial or add-on therapy for hypertension include heart failure, post-myocardial infarction (MI), high coronary disease risk and diabetes.[12] Many of the national and international organizations include β-blocker combination products in their lists of medications, but do not establish a preference for one particular agent over another.[17-22] Combination products are generally not used as initial therapy and are reserved until the desired effects have been met upon titration of the individual components.[17] For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 3. Treatment Guidelines Using the Combination β-Adrenergic Blocking Agents

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)[17]**	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium-channel blocking agents (CCBs). This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • In patients with acute coronary syndromes (ACS) (MI or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. Other medications may be used as needed for blood pressure control. • For patients with post-MI, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial.

Clinical Guideline	Recommendation
	• For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients. • Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators. • β-Blockers are useful in the treatment and/or prophylaxis of atrial arrhythmias/fibrillation, migraine, thyrotoxicosis (short term), essential tremor, and perioperative hypertension. • β-Blockers should be used cautiously or avoided in patients with asthma, reactive airways disease, or second or third degree heart block. • Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • Thiazide diuretics are useful in slowing demineralization in osteoporosis.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)[18]**	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors). • A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)[19]**	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy

Clinical Guideline	Recommendation
	(methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[20]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients. • Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[21]	• β-blockers are generally not preferred for initial therapy for hypertension, though they may be used in younger patients in the case of ACE inhibitor and ARB intolerance, in women of childbearing age, and in patients with an increased sympathetic drive. • If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes). • Patients who are well-controlled on a β-blocker do not need to be switched from the β-blocker to an alternative agent. • If a β-blocker is to be discontinued, the dose should be gradually decreased. β-blockers should not be discontinued in patients who have a compelling indication for β-blockade, including those with angina and those who have had an MI. • Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[22]	• No specific recommendation is made concerning combination β-blockers.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[23]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2. • Multiple drug therapy is generally required to achieve blood pressure goals.

Clinical Guideline	Recommendation
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[24]	• ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic. • All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • CCBs and thiazide diuretics may be more effective than other drug classes in African Americans.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[25]	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals. • All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence. • Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible.

III. Indications

The Food and Drug Administration (FDA)-approved indications for combination β-adrenergic blocking agents (β-blockers) are listed in Table 4. Per the package inserts, these fixed combinations are not indicated for the initial therapy of hypertension and the separate agents should be titrated to the individual patient. Once stable on the individual components, these agents may be used for the management of the patient.[1-6] 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 Combination β-Adrenergic Blocking Agents[1-6]

Drug(s)	Hypertension
Atenolol and chlorthalidone	✔
Bisoprolol and hydrochlorothiazide	✔
Metoprolol and hydrochlorothiazide	✔
Nadolol and bendroflumethiazide	✔
Propranolol and hydrochlorothiazide	✔
Timolol and hydrochlorothiazide	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the combination β-adrenergic blocking agents (β-blockers) are summarized in Table 5. Each of the package inserts for the combination products lists the pharmacokinetics of the components separately rather than together.[1-6]

Table 5. Pharmacokinetic Parameters of the Combination β-Adrenergic Blocking Agents[13,26-32]

Drug	Bioavailability(%)	Protein Binding (%)	Lipid Solubility	Metabolism	Active Metabolites	Half-Life (hours)
β-Blockers						
Atenolol	50	6-16	Low	Renal	No	6-7
Bisoprolol	80	~30	Low	Renal/hepatic	No	9-12
Metoprolol	50	12	Moderate	Hepatic (CYP2D6)	No	3-7
Nadolol	30	30	Low	Renal	No	20-24
Propranolol	30	90	High	Hepatic (CYP2D6)	Yes	3-5
Timolol	75	<10	Low-Moderate	Renal	No	4
Diuretics						
Bendroflumethiazide	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Chlorthalidone	65 104-116 (with PVP)	75	Not reported	Not reported	No	40-89
Hydrochlorothiazide	50-75	40-68	Not reported	None	No	6-15

PVP=povidone polyvinylpyrrolidone

V. Drug Interactions

Significant drug interactions with the combination β-adrenergic blocking agents (β-blockers) are listed in Table 6.

Table 6. Significant Drug-Drug Interactions with the Combination β-Adrenergic Blocking Agents[16]

Drug(s)	Significance Level	Interaction	Mechanism
Atenolol, metoprolol, nadolol, propranolol, timolol	1	Clonidine	β -Blocker inhibition of β_2 receptor mediated vasodilation leaves peripheral α_2-receptor mediated vasoconstriction unopposed to clonidine stimulation.
Atenolol, metoprolol, nadolol, propranolol, timolol	1	Verapamil	May be synergistic or additive effects. Verapamil may inhibit oxidative metabolism of certain β-blockers.
Nadolol, propranolol, timolol	1	Epinephrine	Nonselective β blockade allows α -receptor effects of epinephrine to predominate. Increasing vascular resistance leads to a rise in blood pressure and reflex bradycardia.

Drug(s)	Significance Level	Interaction	Mechanism
Nadolol, propranolol, timolol	1	Sympathomimetics (albuterol, arformoterol, bitolterol, formoterol, levoalbuterol, salmeterol)	Nonselective β-blockers may block the action of β-agonists, potentially resulting in severe bronchospasm in asthmatics.
Propranolol	1	Phenothiazines (chlorpromazine, thioridazine)	Chlorpromazine may inhibit the first-pass hepatic metabolism of propranolol and increase its pharmacologic effects. Certain β-blockers may inhibit the metabolism of thioridazine.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Atenolol	2	Ampicillin	The bioavailability of atenolol may be decreased by impaired GI absorption induced by ampicillin.
Atenolol, metoprolol, propranolol	2	Diltiazem	Possibly inhibition of oxidative metabolism of β-blockers and additive pharmacologic effects.
Atenolol, metoprolol, nadolol, propranolol	2	Lidocaine	Reduced hepatic lidocaine metabolism and possibly a minor component of diminished hepatic blood flow.
Atenolol, bisoprolol, metoprolol, nadolol, propranolol, timolol	2	Non steroidal antiinflamatory drugs (NSAIDs) (ibuprofen, indomethacin, naproxen, piroxicam)	NSAIDs may inhibit renal prostaglandin synthesis, allowing unopposed pressor systems to produce hypertension.
Atenolol, bisoprolol, metoprolol, nadolol, propranolol, timolol	2	Prazosin	Unknown.
Atenolol, metoprolol, propranolol, timolol	2	Quinidine	Oxidative metabolism of certain β-blockers may be inhibited by quinidine.
Atenolol, bisoprolol, metoprolol, propranolol	2	Rifamycins (rifabutin, rifampin, rifapentine)	Possibly due to increased hepatic metabolism from enzyme induction
Atenolol, bisoprolol, metoprolol, nadolol, propranolol, timolol	2	Salicylates (aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate)	Hypertension: salicylates may inhibit biosynthesis of prostaglandins involved in the antihypertensive activity of β-blockers. Heart failure: unknown.
Metoprolol, propranolol	2	Barbiturates (amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital,	Barbiturates enhance enzyme induction and hepatic first-pass extraction that may reduce oral bioavailability of certain β-blockers.

Drug(s)	Significance Level	Interaction	Mechanism
		pentobarbital, phenobarbital, primidone, secobarbital)	
Metoprolol, propranolol	2	Hydralazine	Hydralazine increases systemic availability of some β-blockers, probably by transient increase in splanchnic blood flow and decreasing first-pass hepatic metabolism.
Metoprolol, propranolol	2	Propafenone	Propafenone increases plasma β-blocker level by decreasing first-pass metabolism and reducing systemic clearance. Both drugs are oxidized by the hepatic cytochrome P450 system, and propafenone appears to inhibit the metabolism of the β-blocker.
Metoprolol, propranolol	2	Thioamines (methimazole, propylthiouracil)	Hyperthyroidism appears to cause increased clearance of β-blockers with a high extraction ration. This may be the result of increased liver blood flow, first-pass metabolism and volume of distribution.
Metoprolol, propranolol, timolol	2	Cimetidine	Cimetidine may reduce hepatic first-pass extraction, decrease liver blood flow, and inhibit hepatic metabolism of propranolol.
Metoprolol, propranolol, timolol	2	Diphenhydramine	Inhibition of CYP2D6-mediated β-blocker metabolism.
Nadolol, propranolol, timolol	2	Ergot derivatives (Dihydroergotamine, ergotamine, methysergide)	Ergot alkaloid mediated vasoconstriction and β-blocker mediated blockade of peripheral β_2 receptors allows for unopposed ergot action.
Nadolol, propranolol, timolol	2	Insulin	β-blockers blunt sympathetic mediated responses to hypoglycemia.
Propranolol	2	Digoxin	May increase digoxin bioavailability. Possible additive depression of myocardial conduction and decreased renal tubular digoxin secretion.
Propranolol	2	Rizatriptan	Inhibition of rizatriptan metabolism (monoamine oxidase-A) by propranolol is suspected.
Propranolol, timolol	2	Theophyllines (aminophylline, dyphylline, oxtriphylline, theophylline)	Pharmacologic antagonism. B-blockers may reduce the n-demethylation of theophylline.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate

Drug(s)	Significance Level	Interaction	Mechanism
			carefully in small or intermittent doses.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

Significant adverse drug events for the combination β-adrenergic blocking agents are listed in Table 7. Black box warnings associated with the combination β-blockers are listed in Tables 8-10. The single entity agent Tenormin® (atenolol) has a Food and Drug Administration (FDA)-issued black box warning regarding the potential of a severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias in patients with coronary artery disease who abruptly discontinue atenolol therapy.[25] Tenoretic®, the combination of atenolol and chlorthalidone, does not have a black box warning listed in the package insert, however the potential for adverse events associated with the abrupt discontinuation of atenolol therapy is addressed in the warnings section.[1] Also, the Lopressor® (metoprolol tartrate) package insert lists a black box warning for ischemic heart disease,[23] but this black box warning is not listed as such in the Lopressor HCT® (metoprolol tartrate/hydrochlorothiazide) package insert, they are addressed in the warning section of the insert.[3]

Table 7. Adverse Drug Events (%) for the Combination β-Adrenergic Blocking Agents[26-35]

Adverse Event	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Timolol	Bendroflume-thiazide	Chlor-thalidone	HCTZ
Cardiovascular									
Angina	-	-	-	-	✔	✔	-	-	-
Arrhythmia	-	<1	-	1	-	1	-	-	-
Arterial/vascular insufficiency/Raynaud's phenomenon	1-10	-	1	2	✔	✔	-	-	-
Atrioventricular nodal disturbances	-	-	-	-	✔	-	-	-	-
Bradycardia	1-10	1	2-16	1-10*	6†	9	-	-	-
Cardiac failure/arrest	-	-	-	1	-	✔	-	-	-
Cardiogenic shock	-	-	✔	-	✔	-	-	-	-
Chest pain	1-10	1-2	-	<1	2-4	1	-	-	-
Cold extremities	1-10	<1	1	1-10	✔	✔	-	-	-
Congestive heart failure	1-10	<1	1	1-10	✔	-	-	-	-
Edema	1-10	4	-	1-10	2	1	-	-	-
Flushing	-	<1	-	-	-	-	-	-	-
Heart block	1-10	-	5	-	-	✔	-	-	-
Hypertension	-	-	-	-	-	-	-	-	-
Hypotension	1-10	<1	1-27	1	✔	✔	-	-	1-10
Myocardial contractility impaired	-	-	-	-	✔	-	-	-	<1
Orthostatic hypotension	-	<1	-	<1	-	-	✔	✔	1-10
Palpitations	-	<1	1	1-10	-	✔	-	-	-
Peripheral circulation reduced	-	-	-	1-10	-	-	-	-	-
Peripheral edema	-	3	1	-	-	-	-	-	-

Adverse Event	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Timolol	Bendroflume-thiazide	Chlor-thalidone	HCTZ
Postural hypotension	2	-	-	-	-	-	-	-	-
Rhythm disturbance	-	<1	-	-	-	-	-	-	-
Shortness of breath	-	-	3	-	-	-	-	-	-
Syncope	-	<1	1	-	-	1	-	-	-
Thrombosis, mesenteric arterial	-	-	-	-	✔	-	-	-	-
Central Nervous System									
Abnormal dreams	-	-	-	-	3	-	-	-	-
Amnesia	-	-	-	-	✔	-	-	-	-
Anxiety	-	<1	✔	-	-	✔	-	-	-
Catatonia	-	-	-	-	✔	-	-	-	-
Cerebral ischemia	-	-	-	-	-	✔	-	-	-
Cerebral vascular accident	-	-	-	-	-	✔	-	-	-
Change in behavior	-	-	-	1	-	-	-	-	-
Cognitive dysfunction	-	-	-	-	✔	-	-	-	-
Confusion	1-10	<1	≥1	<1	✔	✔	-	-	-
Convulsions	-	-	-	-	-	-	-	-	-
Depression	1-10	<1	5	1-10	1-3	✔	-	-	-
Disorientation	-	-	-	-	-	✔	-	-	-
Dizziness	1-10	4	2-10	2	2-11	2	✔	✔	✔
Drowsiness	1	-	-	>10	2	-	-	-	-
Emotional lability	-	-	-	-	✔	-	-	-	-
Fatigue	1-10	6-8	1-10	2	3-17	3	-	-	-
Fever	-	-	-	-	-	-	✔	-	✔
Hallucinations	<1	<1	≥1	<1	✔	✔	-	-	-
Headache	1-10	11	≥1	-	1-9	2	✔	✔	✔
Hyper/ hypoesthesia	-	1-2	-	-	-	-	-	-	-
Insomnia	1-10	2-3	≥1	>10	3-8	✔	-	-	-
Lethargy	1-10	-	-	-	4	-	-	-	-
Lightheadedness	1	-	-	-	✔	-	-	-	-
Malaise	-	<1	-	-	-	-	-	-	-
Memory loss	-	<1	≥1	-	-	✔	-	-	-
Mental impairment	1-10	-	-	-	-	-	-	-	-
Nervousness	-	<1	✔	-	2	✔	-	-	-
Nightmares/vivid dreams	1-10	-	≥1	-	✔	✔	-	-	-
Paresthesia	-	<1	✔	-	-	1	✔	<1	✔
Psychosis	<1	-	-	-	✔	-	-	-	-

Adverse Event	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Timolol	Bendroflume-thiazide	Chlor-thalidone	HCTZ
Sedation	-	-	-	1	-	-	-	-	-
Sleep disturbance	-	<1	≥1	-	-	-	-	-	-
Somnolence	-	<1	≥1	-	✔	✔	-	-	-
Vertigo	2	<1	≥1	-	✔	1	✔	✔	✔
Dermatologic									
Acne	-	<1	-	-	-	-	-	-	-
Alopecia	<1	<1	✔	-	✔	✔	-	-	<1
Cutaneous ulcers	-	-	-	-	✔	-	-	-	-
Dermatitis	-	<1	-	-	✔	-	-	-	-
Ecchymosis	-	-	-	-	-	-	✔	-	-
Eczema	-	<1	-	-	-	-	-	-	-
Eczematous eruptions	-	-	-	-	✔	-	-	-	-
Erythema multiforme	-	-	-	-	✔	-	-	-	✔
Exfoliative dermatitis	-	-	-	-	✔	-	✔	-	✔
Hyperkeratosis	-	-	-	-	✔	-	-	-	-
Nail changes	-	-	-	-	✔	-	-	-	-
Oculomucocutaneous reactions	-	-	-	-	✔	-	-	-	-
Photosensitivity	-	-	≥1	-	-	-	✔	1-10	1-10
Pruritus	-	<1	5	-	✔	1	✔	-	-
Pseudo pemphigoid	-	-	-	-	-	✔	-	-	-
Psoriasiform rash	<1	<1	-	-	✔	✔	-	-	-
Psoriasis (exacerbated)	-	<1	≥1	-	-	✔	-	-	-
Purpura	-	<1	-	-	-	-	✔	<1	✔
Rash	-	<1	5	-	0-2	✔	✔	<1	✔
Stevens-Johnson syndrome	-	-	-	-	✔	-	-	-	<1
Sweating, excessive	-	1	✔	-	2	-	-	-	-
Toxic epidermal necrolysis	-	-	-	-	✔	-	-	✔	<1
Ulcers	-	-	-	-	✔	-	-	-	-
Urticaria	-	-	✔	-	✔	✔	✔	<1	✔
Endocrine and Metabolic									
Alkaline phosphatase increased	-	-	✔	-	✔	-	-	-	-
Diabetes (exacerbated)	-	-	≥1	-	-	-	-	-	-
Glycosuria	-	-	-	-	-	-	✔	✔	✔
Gout	-	<1	-	-	-	-	-	<1	-
Hypercalcemia	-	-	-	-	-	-	-	<1	<1

Adverse Event	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Timolol	Bendroflume-thiazide	Chlor-thalidone	HCTZ
Hyperglycemia	-	<1	-	-	✔	-	-	<1	✔
Hyperkalemia	-	<1	-	-	✔	-	-	-	-
Hyperlipidemia	-	-	-	-	✔	-	-	-	-
Hypernatremia	-	-	-	-	-	-	-	<1	-
Hypertriglyceridemia	-	<1	-	-	-	-	-	-	-
Hyperuricemia	-	-	-	-	-	-	✔	✔	✔
Hypoglycemia	-	-	-	-	✔	-	✔	-	-
Hypoglycemia masked	-	-	-	-	-	✔	-	-	-
Hypokalemia	-	-	-	-	-	-	-	1-10	1-10
Libido decreased	-	-	≥1	-	-	1	-	-	-
Gastrointestinal									
Abdominal bloating	-	-	-	-	-	-	✔	-	-
Abdominal discomfort	-	<1	-	1-10	-	-	-	-	-
Abdominal pain	-	-	1	-	1	-	-	-	-
Angioedema	-	<1	-	-	-	✔	-	-	-
Anorexia	-	-	-	-	✔	✔	✔	1-10	1-10
Constipation	1-10	<1	1	1-10	0-2	-	✔	✔	✔
Cramping	-	-	-	-	✔	-	✔	✔	✔
Diarrhea	1-10	3-4	5	1-10	2-7	✔	✔	✔	✔
Dry mouth	-	1	1	-	-	✔	-	-	-
Dyspepsia	-	<1	-	-	1-7	1	-	-	-
Epigastric distress	-	-	-	-	-	-	✔	1-10	1-10
Flatulence	-	-	1	-	4	-	-	-	-
Gastritis/gastric irritation	-	<1	-	-	-	-	-	✔	✔
Heartburn	-	-	1	-	-	-	-	-	-
Ischemic colitis	-	-	-	-	✔	-	-	-	-
Nausea	1-10	2	1	1-10	1-6	1	✔	-	✔
Peptic ulcer	-	<1	-	-	-	-	-	-	-
Retroperitoneal fibrosis	-	-	✔	-	-	✔	-	-	-
Sialadenitis	-	-	-	-	-	-	✔	-	✔
Stomach discomfort	-	-	-	-	✔	-	-	-	-
Taste disorder	-	<1	✔	-	-	-	-	-	-
Vomiting	-	1-2	≥1	1-10	✔	-	✔	<1	✔
Weight gain	-	<1	✔	-	-	-	-	-	-
Genitourinary									
Cystitis	-	<1	-	-	-	-	-	-	-
Impotence	1-10	<1	✔	-	1	✔	-	✔	✔

Adverse Event	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Timolol	Bendroflume-thiazide	Chlor-thalidone	HCTZ
Libido decreased	-	<1	-	-	-	-	-	-	-
Micturition (frequency)	-	-	-	-	1	-	-	-	-
Oliguria	-	-	-	-	✔	-	-	-	-
Polyuria	-	<1	-	-	-	-	-	-	-
Proteinuria	-	-	-	-	✔	-	-	-	-
Sexual ability decreased	-	-	-	>10	-	-	-	-	-
Hematologic									
Agranulocytosis	-	-	✔	-	✔	-	✔	<1	<1
Anemia (aplastic/hemolytic)	-	-	-	-	-	-	✔	<1	<1
Claudication	-	<1	≥1	-	-	✔	-	-	-
Leukopenia	-	<1	-	<1	-	-	✔	<1	<1
Purpura	-	-	-	-	✔	-	-	-	-
Thrombocytopenia	<1	<1	✔	<1	✔	-	✔	<1	<1
Hepatic									
Hepatic impairment	-	-	-	-	-	-	-	-	<1
Hepatitis	-	-	✔	-	-	-	✔	-	-
Increase liver enzymes	<1	-	-	-	-	-	-	-	-
Jaundice, cholestatic	-	-	-	-	-	-	✔	✔	✔
Transaminases increase	-	<1	✔	-	✔	-	-	-	-
Neuromuscular and Skeletal									
Arthralgia	-	1-10	✔	-	1	-	-	-	-
Arthritis	-	-	✔	-	-	-	-	-	-
Arthropathy	-	-	-	-	✔	-	-	-	-
Asthenia	-	≤ 2	-	-	-	-	-	-	-
Back pain	-	<1	-	-	-	-	-	-	-
Carpal tunnel syndrome	-	-	-	-	✔	-	-	-	-
Hyper/hypoesthesia	-	<1	-	-	-	-	-	-	-
Muscle cramps	-	<1	-	-	-	-	-	-	-
Muscle pain	-	<1	≥1	-	-	-	-	-	-
Muscle spasm	-	-	-	-	-	-	✔	✔	✔
Myalgia	-	-	-	-	1	-	-	-	-
Myasthenia gravis exacerbated	-	-	-	-	-	✔	-	-	-
Myotonus	-	-	-	-	✔	-	-	-	-
Paresthesia	-	-	-	1	✔	1	-	-	-
Polyarthritis	-	-	-	-	✔	-	-	-	-
Restlessness	-	<1	-	-	-	-	✔	✔	✔

Adverse Event	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Timolol	Bendroflume-thiazide	Chlor-thalidone	HCTZ
Toxic Myopathy	-	-	-	-	-	-	-	-	-
Tremor	-	<1	-	-	-	-	-	-	-
Twitching	-	<1	-	-	-	-	-	-	-
Weakness	-	2	-	-	1	1	✔	✔	✔
Ocular									
Abnormal/blurred vision	-	-	≥1	-	3	-	✔	-	✔
Corneal sensitivity decrease	-	-	-	-	-	✔	-	-	-
Cystoid macular edema	-	-	-	-	-	✔	-	-	-
Diplopia	-	-	-	-	-	✔	-	-	-
Dry eyes	-	-	✔	-	✔	✔	-	-	-
Eye irritation	-	-	-	-	-	1	-	-	-
Eye pain	-	<1	-	-	-	-	-	-	-
Hyperemia of conjuctiva	-	-	-	-	✔	-	-	-	-
Keratitis	-	-	-	-	-	✔	-	-	-
Lacrimation, abnormal	-	<1	-	-	-	-	-	-	-
Mydriasis	-	-	-	-	✔	-	-	-	-
Ocular discharge	-	-	-	-	-	✔	-	-	-
Ocular pain	-	-	-	-	-	✔	-	-	-
Ptosis	-	-	-	-	-	✔	-	-	-
Refractive changes	-	-	-	-	-	✔	-	-	-
Visual acuity decreased	-	-	-	-	✔	-	-	-	-
Visual disturbances	-	<1	≥1	-	✔	✔	-	-	-
Xanthopsia	-	-	-	-	-	-	✔	✔	✔
Otic									
Hearing decreased	-	<1	-	-	-	-	-	-	-
Tinnitus	-	<1	≥1	-	-	1	-	-	-
Renal									
Blood urea nitrogen increased	-	<1	-	-	✔	-	-	-	-
Creatinine increase	-	<1	-	-	-	-	-	-	-
Glomerulonephritis (allergic)	-	-	-	-	-	-	✔	-	-
Interstitial nephritis	-	-	-	-	✔	-	-	-	<1
Renal colic	-	<1	-	-	-	-	-	-	-
Renal failure/dysfunction	-	-	-	-	-	-	-	-	✔
Respiratory									
Bronchitis	-	<1	-	-	-	-	-	-	-
Bronchospasm	-	<1	1	1-10	✔	1	-	-	-
Cough	-	3	-	-	1	✔	-	-	-

Adverse Event	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Timolol	Bendroflume-thiazide	Chlor-thalidone	HCTZ
Dyspnea	<1	1-2	1-3	<1	1-6	1	-	-	-
Eosinophilic pneumonitis	-	-	-	-	-	-	-	-	<1
Laryngospasm	-	-	-	-	✔	-	-	-	-
Nasal congestion	-	-	-	-	-	✔	-	-	-
Pharyngitis	-	2	-	-	✔	-	-	-	-
Pneumonitis	-	-	-	-	-	-	✔	-	-
Pulmonary edema	-	-	-	-	✔	✔	-	-	-
Rales	-	-	-	-	-	1	-	-	-
Respiratory failure/distress	-	-	-	-	✔	✔	-	-	<1
Rhinitis	-	3-4	≥1	-	1	-	-	-	-
Sinusitis	-	2	-	-	-	-	-	-	-
Upper respiratory infection	-	5	-	-	5	-	-	-	-
Wheezing	<1	-	1	-	✔	-	-	-	-
Miscellaneous									
Allergy/allergic reaction	-	-	-	-	-	✔	-	-	<1
Anaphylactoid reaction	-	-	-	-	✔	-	✔	-	✔
Cholecystitis	-	-	-	-	-	-	-	<1	-
Cutaneous vasculitis	-	<1	-	-	-	-	-	<1	-
Electrolyte imbalance	-	-	-	-	-	-	-	✔	✔
Gangrene	-	-	✔	-	-	-	-	-	-
Hyperphosphatemia	-	<1	-	-	-	-	-	-	-
Lactate dehydrogenase increased	-	-	✔	-	-	-	-	-	-
Lupus syndrome	<1	-	-	-	✔	✔	-	-	-
Metabolic acidosis	-	-	-	-	-	-	✔	-	-
Necrotizing angiitis	-	-	-	-	-	-	✔	<1	✔
Pancreatitis	-	-	-	-	-	-	✔	<1	<1
Peyronie's disease	<1	<1	<1	-	✔	✔	-	-	-
Positive antinuclear antibody test	<1	<1	-	-	-	-	-	-	-
Uric acid increased	-	<1	-	-	-	-	-	-	-

*Defined as <40 beats/min.
†Defined as <50 beats/min.
- Event not reported or incidence <1%.
✔ Percent not specified.

Table 8. Black Box Warning for Nadolol and Bendroflumethiazide[4]

WARNING
Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction has occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Table 9. Black Box Warning for Propranolol and Hydrochlorothiazide[5]

WARNING
Angina Pectoris: There have been reports of exacerbation of angina and, in some cases, myocardial infarction following abrupt discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced and the patient should be carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

Table 10. Black Box Warning for Timolol and Hydrochlorothiazide[6]

WARNING
Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

VII. Dosing and Administration

The usual dosing regimens for the combination β-adrenergic blocking agents (β-blocker)are summarized in Table 11.

Table 11. Usual Dosing for the Combination β-Adrenergic Blocking Agents[1-6]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Atenolol and chlorthalidone	Hypertension: Initial: 50/25 mg once daily Maintenance: if optimum response is not achieved, may increase to 100/25 mg once daily Renal impairment: Creatinine clearance (Cr_{Cl}) 15 to 35 mL/min; maximum recommended atenolol dose is 50 mg once daily	Safety and efficacy in children have not been established.	Tablet: 50 mg-25 mg 100 mg-25 mg

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Cr_{Cl} 15-35 mL/min; maximum recommended atenolol dose is 25 mg once daily Hepatic Impairment: Use with caution. If adding an additional antihypertensive agent, initiate additional agent at 50% of the recommended initial dose.		
Bisoprolol and hydrochlorothiazide	Hypertension: Initial: 2.5/6.25 mg once daily Maintenance: may titrate dose every 14 days up to 20/12.5 mg once daily Maximum: 20/12.5 mg once daily Hepatic/Renal Impairment: Use with caution. Discontinuation of therapy should occur gradually over about 2 weeks.	Safety and efficacy in children have not been established.	Tablet: 2.5 mg-6.25 mg 5 mg-6.25 mg 10 mg-6.25 mg
Metoprolol and hydrochlorothiazide	Hypertension: Initial: 100/25 mg/day in single or divided doses Maintenance: May titrate dose gradually until desired effect is achieved; usual dose of metoprolol is 100 to 450 mg/day, and of hydrochlorothiazide, 12.5 to 50 mg/day; may be administered in single or divided doses Hepatic/Severe Renal Impairment: Use with caution If adding an additional antihypertensive agent, initiate additional agent a 50% the recommended initial dose. Should not be abruptly stopped.	Safety and efficacy in children have not been established.	Tablet: 50 mg-25 mg 100 mg-25 mg 100 mg-50 mg
Nadolol and bendroflumethiazide	Hypertension: Initial: 40/5 mg once daily Maintenance: if desired effect is not achieved, may increase dose to 80/5 mg once daily Renal Impairment: Cr_{Cl} >50 mL/min: administer every 24 hours Cr_{Cl} 31 to 50 mL/min: administer every 24 to 36 hours Cr_{Cl} 10 to 30 mL/min: administer every 10 to 30 hours Cr_{Cl} <10 mL/min: administer every 40 to 60 hours Hepatic Impairment: Use with caution. If adding an additional antihypertensive agent, initiate additional agent at 50% of the recommended initial dose.	Safety and efficacy in children have not been established.	Tablet: 40 mg-5 mg 80 mg-5 mg

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Discontinuation of therapy should occur gradually over about 1 to 2 weeks.		
Propranolol and hydrochlorothiazide	Hypertension: Initial: 40/25 mg twice daily Maintenance: may gradually increase dose until desired response is achieved up to 160 to 480 mg/day Maximum: 160 mg of propranolol is the maximum recommended dose for the combination product, since maximum dose of hydrochlorothiazide will have been reached Severe Renal Impairment: Use with caution. If adding an additional antihypertensive agent, initiate the additional agent at 50% the recommended initial dose.	Safety and efficacy in children have not been established.	Tablet: 40 mg-25 mg 80 mg-25 mg
Timolol and hydrochlorothiazide	Hypertension: Initial: 20/50 mg/day in single or divided doses Maintenance: 20/50 mg/day in single or divided doses; if optimal response in not achieved, may add an additional nondiuretic antihypertensive agent Renal/Hepatic Impairment: Dose reductions may be necessary. Discontinuation of therapy should occur gradually over about 1 to 2 weeks.	Safety and efficacy in children have not been established.	Tablet: 10 mg-25 mg

VIII. Effectiveness

A evidence-based medicine literature search from 1966 to the present did not reveal clinical trials regarding the combination product of timolol and hydrochlorothiazide or direct comparisons of one combination β-adrenergic blocking agent to another. Clinical studies evaluating the safety and efficacy of the combination β-adrenergic blocking agents (β-blocker) are summarized in Table 12.

Table 12. Comparative Clinical Trials Using the Combination β-Adrenergic Blocking Agents

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lewin et al[36] Bisoprolol 5 mg -HCTZ 6.25 mg/day vs placebo There was a placebo run-in phase.	MC, PC Adult patients with stable mild to moderate (sitting DBP 95 to 114 mm Hg) essential hypertension	N=36 4 weeks	Primary: Changes in 24-hour ambulatory daytime and nighttime blood pressure Secondary: Not reported	Primary: There were statistically significant reductions in blood pressure and pulse (*P*<0.01) at weeks 2 and 4 of treatment. There were statistically significant reductions (*P*<0.01) in 24 hour SBP and DBP, daytime and nighttime blood pressure, compared to the end of the placebo phase. There was a reduction in systolic and diastolic load also (*P*<0.01). The combination was well tolerated. The scores from the overall quality-of-life questionnaire indicated an improvement with the combination (*P*=0.02). Secondary: Not reported
de Leeuw et al[37] Active treatment group: verapamil SR 180 mg-trandolapril 2 mg, atenolol 100 mg-chlorthalidone 25 mg or lisinopril 20 mg-HCTZ 12.5 mg vs placebo There was a single-blind placebo 4-week run in	DB, MC, PC, RCT Patients 18-70 years with essential hypertension (WHO I or II) newly or unsuccessfully treated, with supine DBP 101 to 114 mm Hg in week 4 of the run-in period	N=205 12 weeks	Primary: Changes in supine blood pressure, standing blood pressure response rates, and normalization rates Secondary: Not reported	Primary: Each of the three active treatments was significantly more effective than placebo in reducing in DBP in seated patients. Changes in DBP were as follows: verapamil SR-trandolapril: –13 (95% CI, –16 to –9), atenolol-chlorthalidone –13 (95% CI, –16 to –9), lisinopril-HCTZ –12 (95% CI, –15 to –9) and placebo: –3 (95% CI, –7 to 0); *P*=0.0001 for all groups compared to placebo, but there was not a statistical significance among treatment groups (*P* values were not reported). Each of the three active treatments was significantly more effective than placebo in reducing SBP in seated patients. Changes in SBP were as follows: verapamil SR-trandolapril: –27 (95% CI, –33 to –21), atenolol-chlorthalidone –28 (95% CI, –34 to –22), lisinopril-HCTZ –23 (95% CI, –29 to –17) and placebo: –3 (95% CI, –9 to +3); *P*=0.0001 for all groups compared to placebo, but there was not a statistical

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
period.				significance among treatment groups (*P* values were not reported). Effects on standing blood pressure demonstrated similar results as the effects on sitting blood pressure (actual values and *P* values were not reported). Normalization of DBP (<90 mm Hg), corrected for placebo, were significantly higher in the treatment groups compared to the placebo group: 33% (95% CI, 16% to 50%; *P*<0.0005) of patients in the verapamil SR-trandolapril group, 31% (95% CI, 14% to 48%; *P*<0.002) of patients in the atenolol-chlorthalidone group and 25% (95% CI, 9% to 42%; *P*<0.005) of patients in the lisinopril-HCTZ group. Response rates (normalization of DBP or a reduction in DBP by >10 mm Hg) corrected for placebo were significantly higher in the treatment groups compared to placebo: 40% (95% CI, 22% to 58%; *P*<0.0001) patients in verapamil SR-trandolapril group, 44% (95% CI, 27% to 61%; *P*<0.0001) of patients in the atenolol-chlorthalidone group, and 37% (95% CI, 19% to 55%; *P*<0.0002) of patients in the lisinopril-HCTZ group. Secondary: Not reported
Benetos et al[38] Bisoprolol 2.5 mg-HCTZ 6.25 mg QD vs amlodipine 5 mg QD	DB, MC, PG, RCT Patients over 60 years with supine SBP 160 to 210 mm Hg and DBP <90 mm Hg	N=164 12 weeks	Primary: Changes in blood pressure, heart rate, adverse events and QOL scores Secondary: Not reported	Primary: Both bisoprolol-HCTZ and amlodipine significantly reduced SBP (–20.0±13.7 and –19.6±14.2 mm Hg, respectively; *P*<0.001) and DBP (–4.5±7.4 and –2.4±8.4 mm Hg, respectively from baseline to week 12, but there was not a significant difference between the agents (SBP; *P*=0.85 and DBP; *P*=0.09). Bisoprolol-HCTZ significantly reduced heart rate from baseline, but amlodipine did not (–7.6±8.4 beats/min [*P*<0.001] and –0.2±11.4 beats/min, respectively; [*P* was not reported]). Bisoprolol-HCTZ significantly reduced heart rate when compared to amlodipine (*P*=0.0001).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Overall adverse events were not significantly different between the amlodipine and the bisoprolol-HCTZ group (39% and 40%, respectively; *P* value was not reported). Adverse events reported included headache, leg edema, fatigue and bradycardia but severity of events was not reported. Overall QOL scores were not significantly different between the amlodipine and the bisoprolol-HCTZ group (*P* value was not reported). Secondary: Not reported
Dafgard et al[39] Metoprolol 200 mg-HCTZ 25 mg QAM or HCTZ 50 mg QAM vs HCTZ 25 mg QAM (received during run-in period) There was a single-blind 8-week run-in period where all patients were given HCTZ 25 mg QAM. After run-in period, patients with blood pressure ≥160/95 mm Hg continued on to randomization.	DB, MC, RCT Patients with essential hypertension (WHO stages I or II) not adequately controlled (≥160/95 mm Hg) on HCTZ 25 mg/day	N=31 32 weeks	Primary: To compare the changes in blood pressure, heart rate, adverse events and laboratory values Secondary: Not reported	Primary: After the 8 week run-in period with HCTZ 25 mg alone, the mean supine blood pressure was significantly reduced from 183/110 to 172/103 mm Hg ($P<0.01/P<0.01$). The increased dose of HCTZ 50 mg following the run-in period did not further significantly reduce the mean blood pressure (165/104 mm Hg; *P* values were not reported). A small but statistically significant reduction in supine heart rate was seen when the HCTZ dose was increased from 25 to 50 mg (82 down to 78 beats/min; $P<0.05$). After the 12 week double-blind period, the mean supine blood pressure was 153/98 mm Hg in the HCTZ 50 mg group. After the 12 week follow-up period, there was not any additional decrease in blood pressure (153/97 mm Hg; *P* value was not reported). Combination product of metoprolol and HCTZ produced a significant reduction in supine blood pressure after 12 weeks of therapy from 172/105 mm Hg on HCTZ 25 mg alone to 154/97 mm Hg on the combination therapy ($P<0.001/P<0.01$). Similar results were found with the standing blood pressure reductions, from 165/108 to 147/97 mm Hg ($P<0.001/P<0.001$). After the 8 week run-in period, the supine heart rate was 80 beats/min which decreased to 64 beats/min with the metoprolol-HCTZ combination ($P<0.001$). The values for standing heart rate demonstrated

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				similar significant reductions (85 to 66 beats/min; *P*<0.001). After the additional 12 week follow-up, the patients in the metoprolol-HCTZ combination group did not demonstrate a significant further reduction in heart rate or blood pressure in any position (*P* values were not reported). Both agents were tolerated and the most common adverse events reported included insomnia, headache, tiredness, and shortness of breath. A majority of event s were mild, few were moderate and none were severe (*P* values were not reported). The only significant changes in laboratory values occurred with the HCTZ 25 mg and 50 mg groups, where an increase in serum uric acid was observed from 0.30 to 0.34 and 0.35 mmol/L, respectively; *P*<0.01 and *P*<0.05; respectively). Secondary: Not reported
Frishman, Brysinski, et al[41] Bisoprolol 2, 5, 10, or 40 mg QD vs HCTZ 6.25 or 25 mg once daily vs bisoprolol plus HCTZ, all possible combinations	DB, MC, PC, RCT Patients 21 years and older with mild to moderate essential hypertension whose weight was 35% of the ideal for height and frame and mean sitting DBP was stable and between 95 to 115 mm Hg	N=512 12 weeks	Primary: Changes in DBP and SBP Secondary: Not reported	Primary: All treatment groups (all doses) of bisoprolol, HCTZ and the combination of bisoprolol-HCTZ significantly reduced sitting DBP from baseline (*P*<0.01). The reduction in blood pressure was significantly greater as the doses of the bisoprolol, HCTZ and the combination of bisoprolol-HCTZ were increased (*P*<0.05). The combination bisoprolol-HCTZ significantly reduced sitting DBP compared to the separate agents as monotherapy (*P*<0.01). With higher doses of HCTZ, there was a significantly higher incidence of hypokalemia, defined as potassium <3.5 mmol/L (*P*<0.01). Incidence of hyperuricemia also significantly increased with the increase in HCTZ dose (*P*<0.01). Adverse events associated with hypokalemia and hyperuricemia were not reported.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				As the dose of bisoprolol was increased, the frequency and severity of adverse events reported significantly increased (*P*<0.05). Adverse events reported included asthenia, diarrhea, dyspepsia and somnolence, but severity of effects was not reported. Secondary: Not reported
Frishman, Burris, et al[42] Bisoprolol 5 mg QD vs HCTZ 25 mg QD vs bisoprolol 5 mg-HCTZ 6.25 mg QD vs placebo (given during run-in period) There was a 4-6 week placebo run-in period.	DB, MC, PC, PG, RCT Patients ≥21 years with mild to moderate (stage II or II) systemic hypertension whose body weight was not >10% below or 35% above the ideal weight for height and frame, and were off all antihypertensive medications before study entry and sitting DBP was 95 to 115 mm Hg on 3 consecutive weekly visits	N=547 10 weeks	Primary: Changes in blood pressure and adverse events Secondary: Not reported	Primary: All active treatment groups significantly reduced sitting DBP and SBP from baseline compared to placebo (*P*<0.01). Addition of HCTZ 6.25 mg contributed significantly to the blood pressure lowering effects of bisoprolol 5 mg (*P* values were not reported). The combination bisoprolol 5 mg-HCTZ 6.25 mg produced a significantly greater reduction in mean sitting DBP from baseline (-12.6±0.5 mm Hg) than bisoprolol 5 mg alone (-10.5±0.5 mm Hg; *P*=0.02) and HCTZ 25 mg alone (-8.5±0.5 mm Hg; *P*<0.01). Bisoprolol 5 mg monotherapy was significantly better a reducing DBP compared to HCTZ 25 mg alone (*P*=0.03). The combination bisoprolol 5 mg-HCTZ 6.25 mg produced a significantly greater reduction in mean sitting SBP from baseline (-15.8 mm Hg) than bisoprolol 5 mg alone (-10 mm Hg; *P*<0.01) and HCTZ 25 mg alone (-15.8 mm Hg; *P*<0.01). There was not a significant difference in mean reduction between bisoprolol 5 mg alone and HCTZ 25 mg alone (*P* value was not reported). Bisoprolol 5 mg and HCTZ 6.25 mg in combination had a 73% response rate compared to 61% for the bisoprolol group and 47% for the HCTZ group (*P* values were not reported). Bisoprolol 5 mg and HCTZ 6.25 mg in combination was found to be significantly more effective than bisoprolol 5 mg or HCTZ 25 mg in all subgroups of patients regardless of age, race, gender, or smoking history (*P*>0.05 for all comparisons).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Bisoprolol 5 mg and HCTZ 6.25 mg in combination did not have an increase in frequency or severity of adverse events. The adverse events were comparable to that in the placebo group and frequency among groups was not significant (*P* values were not reported). The most common adverse events reported were headache, dizziness, fatigue and cough. Severity of events was not reported. Significantly greater number patients in the HCTZ 25 mg group (6.5%) experienced hypokalemia (potassium <3.4 mEq/L) compared to the bisoprolol 5 mg group (0.7%; *P*<0.01), the bisoprolol-HCTZ group (0.7%; *P*<0.01) and placebo (0%; *P*<0.01). Hyperglycemia occurred in 7.4% of patients in the HCTZ 25 mg group, which was significantly higher then in the placebo group (5.2%; *P*=0.03). Also, the incidence of hyperuricemia (uric acid >7.5 mg/dL) was significantly higher in the HCTZ 25 mg group (24.4%) compared to placebo (2.7%; *P*<0.01). Secondary: Not reported
Fogari et al[43] Weeks 1-4: Atenolol 50 mg QD vs chlorthalidone 12.5 mg QD Weeks 5-study end: atenolol 50 mg-chlorthalidone 12.5 mg QD There was a 4 week run-in	RCT, SB Patients 61-80 years inadequately controlled (SBP >170 mm Hg and/or DBP >100 mm Hg) on antihypertensive medications	N=38 6 months	Primary: Changes in blood pressure Secondary: Not reported	Primary: After the first 4 weeks, atenolol (from 177.5 to 161.1 mm Hg) significantly reduced blood pressure compared to baseline, but chlorthalidone did not (from 176.6 to 179.1 mm Hg; *P* values were not reported). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to previous therapies (*P*<0.001 for all comparisons). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to atenolol and chlorthalidone monotherapy (*P*<0.001 or *P*<0.01 for all comparisons).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
period during which the patients took their previous antihypertensive treatment.				Mean blood pressure reduction obtained by the atenolol and chlorthalidone combination product was 30/15 mm Hg in the standing position (*P*<0.001). Serum potassium rose significantly with atenolol-chlorthalidone (4.45 mEq/L) compared to chlorthalidone alone (4.01 mEq/L) (difference of 0.44±0.10; *P*<0.001). Secondary: Not reported
Leonetti et al[44] Atenolol 50 mg QD vs atenolol 100 mg QD vs chlorthalidone 12.5 mg QD vs atenolol 50 mg-chlorthalidone 12.5 mg QD There was a 4-week placebo wash-out period.	DB, RCT Patients 24-68 years with mild to moderate hypertension (WHO stage I or II), with supine DBP ≥95 mm Hg at the end of the 4-week washout period	N=28 16 weeks	Primary: Changes in blood pressure Secondary: Not reported	Primary: Mean supine blood pressure was 165±12/102±8 mm Hg for placebo patients. Mean supine blood pressure was significantly reduced in all treatment groups compared to placebo: 153±18/93±9 mm Hg for atenolol 50 mg patients, 155±22/91±8 mm Hg for atenolol 100 mg patients, 148±17/93±11 mm Hg for chlorthalidone 12.5 mg patients, and 144±16/89±6 mm Hg for the atenolol-chlorthalidone combination patients. All of the changes in blood pressure were significant (*P*<0.01) versus placebo. Supine SBP was lower with atenolol-chlorthalidone than with the atenolol 100 mg alone (*P*<0.05). Upright SBP was lower with atenolol-chlorthalidone than with atenolol 50 mg alone (*P*<0.05) and atenolol 100 mg alone (*P*<0.05). Mean supine heart rate was 77±7 bpm after placebo which decreased to 69±10 bpm (*P*<0.01) after atenolol 50 mg, to 67±6 bpm (*P*<0.01) after atenolol 100 mg, to 77±10 bpm (*P*=not significant, was not reported) after chlorthalidone alone. Chlorthalidone alone demonstrated a significant reduction in serum potassium levels compared to placebo (3.88 vs 4.09 mEq/L; *P*<0.05) and no change when the atenolol-chlorthalidone combination was compared to placebo (3.98 vs 4.09; *P*=not significant, value was not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Chlorthalidone alone and atenolol-chlorthalidone demonstrated a significant increase in serum uric acid levels compared to placebo (4.90±1.52 mg/dL, 5.07±1.33 mg/dL, respectively, vs 4.24±1.12 for placebo; *P*<0.05 for both). All treatments were well tolerated. Some adverse events reported included dyspnea, precordial discomfort and cold extremities. Incidence, severity and *P* values were not reported. Secondary: Not reported
Liedholm et al[45] Group A: Metoprolol 100 mg-HCTZ 12.5 mg BID vs Group B: metoprolol 100 mg-HCTZ 25 mg BID There was a 6 week run-in period with metoprolol 100 mg BID. Extended Study: metoprolol 100 mg-HCTZ 12.5 mg, 2 tablets QAM	RCT Patients 18-72 years with mild to moderate essential hypertension (WHO I or II) Extended Study: OL Those patients who participated in the initial trial, had poor blood pressure control on existing antihypertensive therapy, and were being treated with a β-blocker and additional diuretic therapy	N=55 12 weeks Extended Study: N=49 6 months	Primary: Change in blood pressure Secondary: Not reported Extended Study: Primary: Change in blood pressure Secondary: Not reported	Primary: In Group A, there was a significant decrease in supine blood pressure from 189/112 to 172/105 mm Hg with metoprolol monotherapy and further reduction to 148/92 mm Hg with the metoprolol 100 mg-HCTZ 12.5 mg combination group (*P*<0.001/*P*<0.001). In Group B, there was a significant decrease in supine blood pressure from 184/111 to 170/104 mm Hg with metoprolol monotherapy and further reduced to 152/96 mm Hg with metoprolol 100 mg-HCTZ 25 mg combination group (*P*<0.01/*P*<0.05) after 12 weeks (*P* value was not reported). Supine heart rate fell in Group A from 78 to 68 beats/min with metoprolol monotherapy (*P*<0.001). No further heart rate reduction was noted with the metoprolol 100 mg-HCTZ 12.5 mg. In Group B, supine heart rate fell from 76 to 69 beats/min (*P*<0.05). No further heart rate reduction was seen with metoprolol 100 mg-HCTZ 25 mg (*P* value was not reported). In Group A, serum sodium fell from 143 to 140 mmol/L (*P*<0.01). In Group B, serum potassium fell with from 4.4 to 4.0 mmol/L (*P*<0.001). Secondary: Not reported

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Extended Study: Primary: After six months of extended the therapy, there was no further significant reductions in supine or standing blood pressure (*P* values were not reported), but there was a reduction in standing DBP from 97 to 95 mm Hg (*P*<0.05). Secondary: Not reported
Nissinen et al[46] Free combination group: Atenolol 100 mg QD plus chlorthalidone 25 mg QAM vs Fixed combination: atenolol 100 mg-chlorthalidone 25 mg QAM vs placebo There was a 4-week placebo run-in.	DB, RCT Patients with newly diagnosed mild to moderate hypertension (supine DBP 100 mm Hg on ≥3 occasions)	N=23 16 weeks	Primary: Changes in blood pressure and heart rate Secondary: Not reported	Primary: Each of the active drug combinations lowered standing, supine, and post-exercise blood pressure significantly compared to placebo at 2 and 4 weeks (*P*<0.001, *P*<0.01 and *P*<0.05). There was not a statistical difference between the active treatment regimens (*P*=not significant, value was not reported). Each of the active drug combinations lowered standing, supine, and post-exercise heart rate significantly compared to placebo at 2 and 4 weeks (*P*<0.001, *P*<0.01 and *P*<0.05). There was not a statistical difference between the active treatment regimens (*P*=not significant, value was not reported). Side effects did not differ between treatment groups and placebo in terms of frequency or severity. Reported side effects included dizziness, headache and tiredness (*P* values were not reported). Secondary: Not reported
Prisant et al[47] Bisoprolol group: Bisoprolol 2.5 mg-HCTZ 6.25 mg, bisoprolol 5 mg-HCTZ 6.25 mg, or bisoprolol 10 mg-HCTZ	DB, MC, PG, RCT Patients ≥21 years with mild to moderate essential hypertension, (average sitting DBP 95 to 114 mm Hg) each	N=218 17 weeks	Primary: Mean change from baseline in SBP and DBP, lab measurements, adverse events and QOL questionnaire	Primary: Mean decreases in SBP and DBP from baseline were 13.4/10.7 mm Hg for bisoprolol-HCTZ combination patients, 12.8/10.2 mm Hg for amlodipine patients, and 7.3/6.6 mm Hg for enalapril patients. The hypotensive effects were significant for all three groups (*P*<0.001). SBP and DBP mean changes from baseline for the bisoprolol-HCTZ

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
6.25 mg vs Enalapril group: enalapril 5, 10, or 20 mg vs Amlodipine group: amlodipine 2.5, 5, or 10 mg There was a 4 to 5-week placebo wash-out period.	treatment was once daily and titrated to effect		Secondary: Not reported	combination group and the amlodipine group were greater than the change from baseline for the enalapril group (*P*<0.01). Response rates (DBP ≤90 mm Hg or ≥10 mm Hg decrease from baseline) were 71% for the bisoprolol-HCTZ combination group, 69% for the amlodipine group, and 45% for the enalapril group. The response rates for the bisoprolol-HCTZ combination and the amlodipine groups differed significantly from the enalapril group (*P*<0.01). 29% of bisoprolol patients had adverse experiences compared to 42% of amlodipine patients (*P*=0.12). 47% of enalapril patients had adverse experience compared to bisoprolol (*P*=0.04). Adverse events reported included headache, fatigue, peripheral edema and dizziness. Drug related adverse events were 16% for the bisoprolol-HCTZ patients, 21% for the amlodipine patients, and 23% for the enalapril patients. There was no significant difference between the groups (*P* values were not reported). Enalapril demonstrated a mean decrease from baseline of 7.9 mg/dL for total cholesterol (*P*=0.02 vs amlodipine) and 6.6 mg/dL for low-density lipoprotein cholesterol (*P*=0.04 vs amlodipine) which were not significantly different from the increase from the bisoprolol-HCTZ group of 1.7 mg/dL (*P*=0.07 vs enalapril) for total cholesterol and +0.6 mg/dL in low-density lipoprotein cholesterol. However, the increase in triglycerides was highest for bisoprolol-HCTZ-treated patients compared with amlodipine- and enalapril treated patients (*P*=0.08, for bisoprolol-HCTZ vs enalapril). There was not a significant difference from baseline or between treatment groups in quality-of-life scores: +0.9 or the bisoprolol-HCTZ group, +0.5 (1.2) for the amlodipine group and 2.3 for the enalapril group (*P* values were not reported). Secondary: Not reported

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Smilde[48] Group 1: Metoprolol 400 mg QAM for 5 weeks then metoprolol 200 mg-HCTZ 25 mg QAM for 5 weeks vs Group 2: Metoprolol 200 mg-HCTZ 25 mg QAM for 5 weeks then metoprolol 400 mg QAM for 5 weeks Patients received metoprolol 200 mg QD for 5 weeks, and those who DBP ≥95 mm Hg after the 5 weeks were further randomized to a group above.	DB, PG, RCT, XO Patients <65 years with essential hypertension (supine DBP ≥95 mm Hg) not controlled on metoprolol 200 mg alone	N=37 15 weeks	Primary: Changes in DBP, SBP and heart rate Secondary: Not reported	Primary: Both group 1 and 2 significantly reduced DBP (*P*<0.01) from baseline and the two groups were not significantly different from each other (*P* value was not reported). The combination products significantly reduced SBP from baseline (*P*<0.05, *P*<0.01 depending on comparison) Group 2 significantly reduced heart arte at the end of the study compared to baseline (*P*<0.05). Clinically relevant changes in laboratory parameters or mean body weight were not observed between the groups (*P* values were not reported). Secondary: Not reported
Stevens et al[49] Dose-finding phase: Propranolol 80, 160, 240, or 320 mg/day in 2 divided doses vs propranolol 80 mg-HCTZ 50 mg, propranolol 160 mg-HCTZ 50 mg, propranolol 240 mg-HCTZ 50 mg, or	DB, PG, RCT Patients with mild to moderate essential hypertension (DBP 100 to 125 mm Hg)	N=158 25 weeks	Primary: Mean changes of SBP and DB, heart rate, lab values Secondary: Not reported	Primary: After the 12 week dose finding-phase, 94% of patients had a decrease greater than or equal to 10 mm Hg in DBP. The mean SBP and DBP reduced from 158.0 (±17.3)/105.6 (±6.0) mm Hg to 131.5 (±14.4)/86.4 (± 6.7) mm Hg (*P*<0.001). After the 10 week portion of the study, there were significantly greater increases (*P*<0.05) in mean SBP or DBP with propranolol and HCTZ alone vs the combination product of propranolol-HCTZ from the end of the dose-finding to the last four biweekly visits to the mean of those visits, and to the last visit. The mean increases of SBP and DBP at the endpoint were: propranolol, 10.2/6.3 mm Hg; HCTZ 13.1/9.3 mm Hg; propranolol-HCTZ combination product 3/1.5 mm Hg.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
propranolol 320 mg-HCTZ 50 mg/day in 2 divided doses Double-blind phase: combination propranolol-HCTZ vs propranolol vs HCTZ There was a 3 week placebo period.				There was a significant decrease in heart rate as the dose of propranolol was increased thought the trial (*P*>0.30). The only lab value that showed a statistically significant change was serum chloride. The percent of patients that fell outside of the normal range were as follows: propranolol 6/36 (17%), HCTZ 14/37 (38%), and combination 4/28 (14%); *P*<0.05. Secondary: Not reported
Veterans Administration Cooperative Study Group on Antihypertensive Agents[50] Nadolol titrated from 80 to 240 mg QAM vs bendroflumethiazide 5 to 10 mg* QAM vs nadolol-bendroflumethiazide There was a placebo run-	DB, RCT Men 20-69 years with pretreatment DBP of 95 to 114 mm Hg	N=365 12 weeks	Primary: Changes in blood pressure, change in blood pressure among races, heart rate, adverse events and laboratory values Secondary: Not reported	Primary: DBP of <90 mm Hg was achieved in 49% of the nadolol patients, 46% of the bendroflumethiazide patients, and 85% of the combination patients. There was a significantly higher percentage of patients who achieved the DBP goal compared to the nadolol alone group and bendroflumethiazide group alone (*P*<0.01 for both). The reduction in SBP was significantly greater in the combination group compared to the nadolol alone and bendroflumethiazide group (-25.3±1.4, -10.5±1.6, and -17.4±1.7 mm Hg, respectively; *P*<0.001 for both) and bendroflumethiazide produced a significantly greater reduction compared to nadolol alone (*P*<0.01). The reduction of DBP in white patients was significantly greater then the decrease in African American (decrease of 15.6 vs 9.6 mm Hg, respectively; *P*<0.001). In addition, 77% of white patients achieved DBP of <90 mm Hg compared to only 31% of African American patients (*P*<0.001).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in period of 2-8 weeks.				Adverse events were infrequent. The most common were impotence, lethargy, weakness and postural dizziness, which occurred more often with bendroflumethiazide than nadolol (*P* values were not reported). Significant reductions in average heart rate from baseline were observed with nadolol alone (decrease by 16.1 beats/min; *P*<0.001) and with the combination product (decrease by15.8 beats/min; *P*<0.001). Serum potassium levels significantly decreased from baseline in the bendroflumethiazide group by -0.57±0.06 mEq/L (*P*<0.001) and in the combination group by -0.44±0.05 mEq/L (*P*<0.001). Serum uric acid levels significantly increased from baseline in the bendroflumethiazide group by 1.7±0.2 mg/dL (*P*<0.001), in the nadolol group by 0.4±0.1 mg/dL (*P*<0.01) and in the combination group by -1.9±0.1 mg/dL (*P*<0.001). Fasting glucose levels significantly increased from baseline in the bendroflumethiazide group by 6.1±2.1 mg/dL (*P*<0.001) and in the combination group by 7.4±1.1 mg/dL (*P*<0.001). Cholesterol significantly increased from baseline in the bendroflumethiazide group by 11.5±4.3 mg/dL (*P*<0.001). Triglycerides significantly increased from baseline in the bendroflumethiazide group by 34.6±14.8 mg/dL (*P*<0.01), in the nadolol group by 38.7±13.2 mg/dL (*P*<0.01) and in the combination group by 67.8±11.9 mg/dL (*P*<0.001). Secondary: Not reported
VA Cooperative Study[51] Propaserp group: Propranolol 40 to 160 mg TID (P), propranolol 40 to 160 mg TID plus HCTZ	DB, RCT Men 18 to 59 years with DBP of 90 to 114 mmHg	N=450 18 months	Primary: Percent of patients who achieved a DBP <90 mmHg at 6 months, heart rate and	Primary: At 6 months, significantly more patients in the R+T arm (88%) attained a DBP <70 mm Hg compared to the P arm (52%; *P*<0.01) and the P+H arm (72%; *P*<0.05). The other arms: P+T (81%) and P+T+H (92%) were not significantly different than the R+T arm.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
35 mg (P+T), propranolol 40 to 160 mg TID plus hydralazine 35 mg (P+H) or propranolol 40 to 160 mg TID plus HCTZ 35 mg plus hydralazine 35 mg (P+T+H) vs Hydrazide group: reserpine 35 mg plus HCTZ 35 mg (R+T)			withdrawal rate Secondary: Not reported	Statistical significance was not maintained at 12 and 18 months, partly due to the low number of patients who remained in the study. R+T=89.1 and 82.6%, P=59.5 and 58.1%, P+T=86.0 and 86.4%, P+H=67.4 and 76.1%, and P+T+H=89.4 and 91.8%; *P* values were not reported. There was not a significance difference in heart rate reductions at 6 months and 18 months between the groups (R+T=5.0±1.3 and 5.0±1.3 mean change in heart rate, P=9.1±1.3 and 9.2±1.8, P+T=8.8±1.2 and 6.3±1.5, P+H=8.9±1.3 and 7.8±1.5, and P+T+H=5.9±1.1 and 7.7±1.5; *P* values were not reported). Withdrawals for any reason were similar between the treatment arms and were not statistically significant (R+T=14 patients, P=11, P+T=12, P+H=14, and P+T+H=16; *P* values were not reported). There were 2 fatal events, 1 cerebral hemorrhage and 1 sudden death both in the P+T groups. Reductions in serum potassium and increases in serum uric acid levels occurred in more patients receiving HCTZ in their regimens compared to those patients who did not receive HCTZ (*P* values were not reported). The most frequent adverse events reported were headache, vertigo, nasal stuffiness and lethargy, but there was not a preponderance of 1 regimen over another. Severity of events and *P* values were not reported. Secondary: Not reported

*Agent is not longer manufactured in the Unites States
Drug regimen abbreviations: BID=twice a day, HCTZ=hydrochlorothiazide, QAM=every morning, QD=everyday, TID=three times a day
Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial, SB=single-blind, XO=cross over
Other abbreviations: β-blockers=β-adrenergic blocking agents, bpm=beats per minute, CCBs=calcium channel blocking agents, DBP=diastolic blood pressure, QOL=quality of life, SBP=systolic blood pressure, SR=sustained release, WHO=World Health Organization

Additional Evidence

Dose Simplification
All of the combination β-adrenergic blocking agents (β-blocker) are given once daily except for the combination product of propranolol-hydrochlorothiazide, which is given twice daily. The combination metoprolol-hydrochlorothiazide and the combination timolol-hydrochlorothiazide may also be given in divided doses.[1-6] In a randomized, double-blind, within-patient study by Nissinen and Tuomilehto, 23 newly diagnosed hypertensive patients received atenolol 100 mg and chlorthalidone 25 mg given in free and fixed combination. Each of the active drug combinations lowered standing, supine, and postexercise blood pressure significantly. There was no statistical difference reported between the active treatment regimens.[46]

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Combination β-Adrenergic Blocking Agents

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
atenolol and chlorthalidone	tablet	Tenoretic®*	$$	$
bisoprolol and hydrochlorothiazide	tablet	Ziac®*	$$	$
metoprolol and hydrochlorothiazide	tablet	Lopressor HCT®*	$-$$	$$
nadolol and bendroflumethiazide	tablet	Corzide®*	$$$	$$$
propranolol and hydrochlorothiazide	tablet	Inderide®*	$$$	$
timolol and hydrochlorothiazide	tablet	Timolide®	$$	N/A

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

X. Conclusions

The combination β-adrenergic blocking agents (β-blocker) are all approved for the treatment of hypertension.[1-6] The effectiveness of these products for the treatment of hypertension was demonstrated through clinical trials. Many of these studies compared a combination β-adrenergic blocking agent to placebo, other antihypertensive medications, one of the single components of the combination, or both of the single components given concurrently. [36-51] When the combination product was compared to one of the single components in the combination product, an additive blood pressure reduction was routinely seen.[41,42,44,48-50] In one of the studies, with atenolol and chlorthalidone, there were no statistical differences in blood pressures when the combination agent was given versus the single components given concurrently.[46]

The combination β-adrenergic blocking agents share many drug-to-drug interactions and common adverse events. The most common adverse events are bradycardia, orthostatic hypotension, dizziness, fatigue, photosensitivity, hypokalemia, anorexia, diarrhea, epigastric distress, nausea, and dyspnea.[27-35] A few clinical studies reported that the lower dose of hydrochlorothiazide, 6.25 mg, in the combination bisoprolol and hydrochlorothiazide products was associated with a lower incidence of hypokalemia than was seen with the 25 mg/day dose included in some of the other products.[41,42] All of the combination β-adrenergic blocking agents are contraindicated in patients with sinus bradycardia, second and third degree heart block, cardiogenic shock, overt cardiac failure, anuria, and hypersensitivity to this product or to sulfonamide-derived drugs. The combination β-adrenergic blocking agents containing nadolol, propranolol and timolol are also contraindicated in patients with bronchial asthma.[1-6]

Current national and international guidelines generally do not recommend combination β-adrenergic blocking agents as initial therapy; however, they do recognize many patients may require more than one antihypertensive medication to achieve blood pressure goals and combination β-adrenergic blocking agents are appropriate choices for antihypertensive treatment. They do not recommend one particular combination β-adrenergic blocking agent over another.[17-25] There are no studies that have demonstrated differences in clinical outcomes when the agents were administered as separate agents concurrently versus a combination product.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand combination β-adrenergic blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agent.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Dihydropyridines
Single Entity Agents
AHFS Class 242808
September 10, 2008

I. Overview

Calcium-channel blocking agents (also called calcium-channel blockers or CCBs) have multiple roles in treating cardiovascular disease. The movement of calcium ions (Ca^{2+}) is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac muscle and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.[1-3] Calcium-channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked, which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance.[4,5] In addition, calcium-channel blocking agents decrease peripheral vascular resistance by relaxing arteriolar smooth muscle.[6] Both coronary and systemic vasodilation serve to reduce cardiac workload.[7] There are two classes of CCBs: dihydropyridines, which are similar in chemical structure, and nondihydropyridines, which are a structurally miscellaneous group. The nondihydropyridines have additional effects and thus a somewhat different therapeutic profile from the dihydropyridines.[1,4,8,9] The nondihydropyridine CCBs, diltiazem and verapamil, will be covered in a separate review, American Hospital Formulary Service (AHFS) Class 242892, Miscellaneous Calcium-channel Blocking Agents.

Dihydropyridines are more potent vasodilators than nondihydropyridines, due to greater selectivity for vascular smooth muscle.[1] They have a lesser effect, or even no effect, upon cardiac muscle contractility or conduction. All available dihydropyridine agents can be used in the treatment of hypertension, with the exception of nimodipine. Although not recommended as first-line therapy for hypertension, the dihydropyridines are generally effective and comparable in their antihypertensive effectiveness, but differ somewhat in other properties and effects. In addition to treating hypertension, amlodipine, oral nicardipine and long-acting nifedipine are effective treatment options for chronic stable angina. Short-acting agents, such as short-acting nifedipine, should be avoided due to increased cardiovascular and mortality risks in some patients as well as significant adverse effects, such as reflex tachycardia.[3]

The dihydropyridine CCBs are available in both immediate-release formulations and in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action. There are numerous generic products available, including generic equivalents for almost all of the dihydropyridines. Since the last review of this class in May 2006, generics have become available for amlodipine and nimodipine.

The single-entity dihydropyridine calcium-channel blocking agents included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Single Entity Dihydropyridines Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
amlodipine	tablet	Norvasc®*	amlodipine
felodipine	sustained-release tablet	Plendil®*	felodipine
isradipine	capsule, sustained-release tablet	DynaCirc®†*, DynaCirc CR®	DynaCirc CR®, isradipine
nicardipine	capsule, injection, sustained-release capsule	Cardene®*, Cardene SR®	nicardipine
nifedipine	capsule, sustained-release tablet	Adalat CC®*, Procardia®*, Procardia XL®*	nifedipine

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
nimodipine	capsule	Nimotop®*	nimodipine
nisoldipine	sustained-release tablet	Sular®	none

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.

II. Evidence-based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the single entity dihydropyridines are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of acute myocardial infarction, angina pectoris, chronic heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Single Entity Dihydropyridines

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[10]	• Long-acting calcium-channel blocking agents (CCBs) or long-acting nitrates may be used if β-adrenergic blocking agents (β-blockers) are contraindicated. Immediate-release and short-acting dihydropyridine CCBs can increase adverse cardiac events and should not be used. • Long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful.
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[11]	• Nitrates, morphine, β-blockers, CCBs, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet agents, and GP IIb/IIIa receptor antagonists can be used in the acute setting during early hospitalization. • CCBs are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. • Treatment with nitrates and CCBs is recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions. • Nitrates, β-blockers, and CCBs (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)**[7]	<u>Therapy to Improve Prognosis</u> • CCBs may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction (MI) and who do not have heart failure. <u>Symptomatic Treatment and Treatment of Ischemia</u> • If patients are intolerant to β-blocker therapy, consideration may be given to a CCB or a long-acting nitrate. Sinus node inhibition may be considered. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. If combination β-blocker and CCB therapy is insufficient, a long-acting nitrate may be substituted for the CCB. <u>Treatment of Syndrome X</u> • Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination. <u>Treatment of Vasospastic/Variant Angina</u> Treatment with CCBs is recommended. Nitrates may also be used if needed.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation**	• CCBs may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina. • Nondihydropyridine CCBs should not be used unless combined with β-blockers.

Clinical Guideline	Recommendation
Acute Coronary Syndromes (NSTE ACS) (2007)[12]	
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease (2004)[13]**	Symptomatic Patients • The following agents are recommended to reduce symptoms only: nitroglycerine (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when monotherapy has been unsuccessful.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)[14]**	Patients With Cardiac Structural Abnormalities or Remodeling Who Have not Developed Heart Failure Symptoms (Stage B) • CCBs with negative inotropic effects are not recommended in asymptomatic patients with low ejection fraction after an MI. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Drugs known to adversely affect patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction (nonsteroidal anti-inflammatory drugs (NSAIDs), some CCBs, some antiarrhythmic medications) should be discontinued and avoided if possible. • CCBs are not recommended as routine treatment for heart failure. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • β-Blockers, angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)[15]**	Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • CCBs should be considered in patients who have hypertension (amlodipine should be considered) or angina, and in those who have atrial fibrillation requiring ventricular rate control and are intolerant to β-blockers. Patients With Heart Failure and Coronary Artery Disease • CCBs should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. Managing Patients With Heart Failure and Hypertension • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or CCB. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent. • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing CCB (amlodipine) may be considered.
European Society of Cardiology (ESC): **Guidelines for the**	• The CCBs diltiazem and verapamil are not recommended in patients with heart failure caused by systolic dysfunction. The addition of felodipine or amlodipine does not improve survival or symptoms, though may be helpful in patients with

Clinical Guideline	Recommendation
Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)[16]	angina or arterial hypertension not controlled with nitrates and β-blockers.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[17]	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting CCBs may also be used. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2 to 4 times higher in African American patients. • CCBs may be useful in Raynaud's syndrome and certain arrhythmias.ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[18]	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[19]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.

Clinical Guideline	Recommendation
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[20]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[21]	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[22]	• No specific recommendation is made concerning single entity dihydropyridines.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[23]	• No specific recommendation is made concerning single entity dihydropyridines.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[24]	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[25]	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of**	• No specific recommendation is made concerning single entity dihydropyridines

Clinical Guideline	Recommendation
Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)[26]	
National Institute for Health and Clinical Excellence (NICE): **Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)[27]**	• Calcium-channel blocking agents (CCBs) should not routinely be used to reduce cardiovascular risk after an MI. • Verapamil or diltiazem may be considered for secondary prevention in patients without pulmonary congestion or left ventricular systolic dysfunction in whom β-blockers must be discontinued or in whom β-blockers are contraindicated.
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)[28]**	Prophylactic Therapies in the Acute Phase • There is no case for using CCBs for prophylactic purposes in the acute phase of an MI. Secondary Prevention • Diltiazem or verapamil may be appropriate if β-blockers are contraindicated in the absence of heart failure. • Dihydropyridines have not been shown to improve prognosis and should only be used for clear clinical indications.

III. Indications

Food and Drug Administration (FDA)-approved indications for the single entity dihydropyridines 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 Single Entity Dihydropyridines [29-42]

Drug	Chronic Stable Angina	Hypertension	Subarachnoid Hemorrhage*	Vasospastic Angina (Prinzmetal's or Variant Angina)
Amlodipine	✔ *	✔ †		✔ *
Felodipine		✔ †		
Isradipine		✔ ‡		
Nicardipine, oral	✔ §	✔ †		
Nicardipine IV		✔ ‖		
Nifedipine	✔ ¶	✔ †#		✔ ¶
Nimodipine			✔ **	
Nisoldipine		✔ †		

IV=intravenous
*Alone or in combination with other antianginal agents.
†Alone or in combination with other antihypertensive drugs.
‡As monotherapy or concurrently with thiazide-type diuretics.
§Immediate Release only; alone or in combination with β-adrenergic blocking agents.
‖Short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, patients should be transferred to oral medication as soon as their clinical condition permits.
¶Except Adalat CC®.
#The immediate-release formulation is not indicated for hypertension.
**Indication for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V).

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity dihydropyridines are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Single Entity Dihydropyridines [29-49]

Drug	Bio-availability (%)	Protein Binding (%)	Active Metabolites	Elimination	Half-Life (hours)
Amlodipine	64-90	93	none	Urine (10% of parent compound and 60% of inactive metabolites)	30-50
Felodipine	20	>99	none	Urine (70%), feces (10%)	11-16
Isradipine	15-24	95	none	Urine (60%-65%), feces (25%-30%)	8
Nicardipine IR	35	>95	none	Urine (60%), feces (35%)	≤8
Nicardipine ER	35	>95	none	Urine (60%), feces (35%)	8-12
Nicardipine IV	100	>95	none	Urine (49%), feces (43%)	2
Nifedipine IR	40-77	92-98	none	Urine (80%)	2
Nifedipine ER	65-89*	92-98	none	Urine (60%-80%), feces (20%-40%)	2
Nimodipine	13	>95	none	Urine (50%), feces (32%)	1-2
Nisoldipine	5	>99	1%-10% of parent	Urine (60%-80%)	7-12

ER=extended-release, IR=immediate release, IV=intravenous
* Percent of immediate release product.

V. Drug Interactions

Significant drug interactions with the single entity dihydropyridines are noted in Table 5.

Table 5. Significant Drug-Drug Interactions with the Single Entity Dihydropyridines [50]

Drug(s)	Significance Level	Interaction	Mechanism
Dihydro-pyridines (felodipine, nicardipine, nifedipine, nimodipine, nisoldipine)	2	Grapefruit juice	Dihydropyridine serum levels may increase due to decreased metabolism resulting from inhibition of CYP3A by grapefruit juice. Coadministration should be avoided.
Felodipine	2	Azole antifungals (itraconazole, ketoconazole, posaconazole, voriconazole)	Felodipine serum levels may increase resulting from decrease metabolism due to CYP3A4 inhibition by azole antifungal agents. Close monitoring of cardiovascular status is recommended.
Felodipine	2	Barbiturates (amobarbital, butabarbital, butalbital, mephobarbital, pentobarbital, phenobarbital, primidone, secobarbital)	Felodipine serum levels may decrease due to induced metabolism of felodipine by barbiturates. Close monitoring of cardiovascular status is recommended, and increased dose of felodipine may be required if long-term coadministration is required.
Felodipine	2	Carbamazepine	Felodipine serum levels may decrease due to induction and increased first-pass metabolism of felodipine, caused by carbamazepine. Close monitoring of cardiovascular status is recommended, and increased dose of felodipine may be required if long-term coadministration is required.
Felodipine	2	Erythromycin	Felodipine serum levels may increase due to inhibition of

Drug(s)	Significance Level	Interaction	Mechanism
			CYP3A by erythromycin. Close monitoring of cardiovascular status is recommended.
Felodipine	2	Hydantoins (ethotoin, fosphenytoin, phenytoin)	Felodipine serum levels may decrease due to increased first-pass metabolism of felodipine caused by hydantoins. Close monitoring of cardiovascular status is recommended, and increased dose of felodipine may be required if long-term coadministration is required.
Nicardipine	2	Cyclosporine	Cyclosporine serum levels may increase due to inhibited metabolism by nicardipine. Cyclosporine levels and renal function should be monitored closely if drugs are coadministered.
Nifedipine	2	Barbiturates (amobarbital, butabarbital, mephobarbital, pentobarbital, phenobarbital, primidone, secobarbital)	Nifedipine serum levels may decrease due to induced metabolism of nifedipine by barbiturates. Close monitoring of cardiovascular status is recommended, and increased dose of felodipine may be required if long-term coadministration is required.
Nifedipine	2	Cisapride	Nifedipine serum levels may increase due to increase absorption of nifedipine, due to increased GI motility caused by cisapride. Close monitoring is recommended and nifedipine doses may need to be adjusted.
Nifedipine	2	Cimetidine	Nifedipine serum levels may increase due to decreased metabolism resulting from inhibition of CYP3A by grapefruit juice. Coadministration should be avoided.
Nifedipine	2	Rifamycins (rifabutin, rifampin, rifapentine)	Nifedipine effects may be decreased due induced metabolism of nifedipine by CYP3A4, which is induced by rifamycins.
Nifedipine	2	Tacrolimus	Tacrolimus serum levels may be elevated due to inhibition of metabolism by nifedipine. Close monitoring of tacrolimus levels and renal function is recommended if coadministered.
Nisoldipine	2	Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Nisoldipine serum levels may increase resulting from decreased metabolism due to CYP3A4 inhibition by azole antifungal agents. Close monitoring of cardiovascular status is recommended.
Nisoldipine	2	Hydantoins (ethotoin, fosphenytoin, mephenytoin, phenytoin)	Nisoldipine serum levels may decrease due to increased first-pass metabolism of nisoldipine caused by hydantoins. Close monitoring of cardiovascular status is recommended, and increased dose of felodipine may be required if long-term coadministration is required.

Significance Level 2=moderate severity.

VI. Adverse Drug Events

Adverse drug reactions for the single entity dihydropyridines are noted in Table 6. One dihydropyridine, nimodipine, has a black box warning regarding parenteral administration; it is reproduced in Table 7.

Table 6. Adverse Drug Events (%) Associated with the Single Entity Dihydropyridines[29-42]

Adverse Event(s)	Amlod-ipine	Felod-ipine	Israd-ipine	Nicard-ipine	Nifed-ipine	Nimod-ipine	Nisold-ipine
Cardiovascular							
Angina (increased)	-	-	-	5.6	-	-	2.0
Arrhythmia	-	0.5-1.5	-	-	-	-	-
Atrial fibrillation	-	-	0.5-1.0	<0.4	-	-	-
Bradycardia	-	-	-	-	-	0.0-1.0	-
Cardiac failure	-	-	0.5-1.0	-	-	-	-
Cerebrovascular accident	-	-	-	-	-	-	1.0
Chest pain	-	0.5-1.5	-	-	-	-	-
Electrocardiogram abnormalities	-	-	-	0.6-1.4	-	0.0-1.4	-
Epistaxis	-	-	0.5-1.0	-	-	-	-
Erythromelalgia	-	-	-	-	1.0	-	-
Extrasystoles (ventricular)	-	-	-	0.7* (1.4)*	-	-	-
Hemopericardium	-	-	-	0.7*	-	-	-
Hypertension	-	-	-	0.7*	-	-	-
Hypotension	-	0.5-1.5	0.5-1.0	5.6*	5	1.2-50	-
Myocardial infarction	-	0.5-1.5	0.5-1.0	<0.4	✔	-	-
Orthostatic hypotension	-	-	-	-	-	-	1.0
Palpitations	0.7-4.5	0.4-2.5	1.0-5.1	2.8-4.1	<2-7	-	3.0
Pericarditis	-	-	-	1.0	-	-	-
Peripheral ischemia	1.0	-	-	✔	-	-	-
Postural hypotension	-	-	-	0.9-1.4	-	-	-
Pulse irregularity	-	0.5-1.5	-	-	-	-	-
Rebound vasospasm	-	-	-	-	-	1.0	-
Tachycardia	-	0.5-1.5	1.0-3.4	1.2-3.5	-	0.0-1.4	-
Vasculitis	1.0	-	-	-	-	-	-
Vasodilatation/vasodilation	-	-	-	0.7-4.7	-	-	4.0
Ventricular fibrillation	-	-	0.5-1.0	-	1.0	-	-
Ventricular tachycardia	1.0	-	-	<0.4 (0.7*)	-	-	-
Central Nervous System							
Abnormal dreams	1.0	-	-	-	-	-	-
Agitation	1.0	-	-	-	-	-	-
Amnesia	1.0	-	-	-	-	-	-
Anxiety	-	0.5-1.5	-	✔	-	-	-
Apathy	1.0	-	-	-	-	-	-
Asthenia	-	2.2-3.9	0.7-5.8	-	<3.0	-	-
Ataxia	-	-	-	-	1.0	-	-
Confusion	-	-	-	✔	-	-	-
Depersonalization	1.0	-	-	-	-	-	-
Depression	-	0.5-1.5	0.5-1.0	✔	1.0	0.0-1.4	-
Dizziness	1.1-3.4	2.7-3.7	3.4-8.0	1.4-6.9	4.1-27	-	5
Headache	7.3	10.6-14.7	10.3-22.0	6.2-14.6	10-23	0.0-1.4	22
Hypoesthesia	-	-	-	0.7*	-	-	-
Insomnia	-	0.5-1.5	0.5-1.0	0.6	<3.0	-	-
Intracranial hemorrhage	-	-	-	0.7*	-	-	-
Irritability	-	0.5-1.5	-	-	-	-	-
Migraine	-	-	-	-	1.0	-	1.0
Nervousness	1.0	0.5-1.5	0.5-1.0	0.6	<2-7	-	-
Paresthesia	-	1.2-1.6	0.5-1.0	0.7-1.0	<3.0	-	-
Peripheral neuropathy	1.0	-	-	-	-	-	-
Sleep disturbance	-	-	-	-	<2.0	-	-

Adverse Event(s)	Amlod-ipine	Felod-ipine	Israd-ipine	Nicard-ipine	Nifed-ipine	Nimod-ipine	Nisold-ipine
Somnolence	0.3-1.6	0.5-1.5	-	1.1-1.4	<3.0	-	-
Stroke	-	-	0.5-1.0	-	-	-	-
Syncope	-	0.5-1.5	0.5-1.0	0.7-0.8	-	-	-
Transient ischemic attack	-	-	0.5-1.0	-	-	-	-
Tremor	-	-	-	0.6	<1-8.0	-	-
Vertigo	1.0	-	-	✔	1.0	-	-
Dermatologic							
Acne	-	-	-	-	-	0.0-1.4	-
Alopecia	-	-	-	-	<1	-	-
Cold and clammy skin	1.0	-	-	-	-	-	-
Dermatitis	-	-	-	-	0.5-2	-	-
Erythema	-	0.5-1.5	-	-	-	-	-
Erythema multiforme	1.0	-	-	-	-	-	-
Flushing	0.7-2.6	3.9-6.9	1.2-5.1	5.6-9.7	<3-25	-	-
Hyperhidrosis/increased sweating	-	-	0.5-1.0	10.6-.4	<2.0	-	-
Pruritus	1.0	-	0.5-1.0	-	<2.0	1.0	-
Rash (erythematous or maculopapular)	-	0.2-2.0	0.0-2.6	0.4-1.2.0	<3.0	0.6-2.4	2.0
Skin discoloration	1.0	-	-	-	-	-	-
Skin dryness	1.0	-	-	-	-	-	-
Urticaria	1.0	0.5-1.5	0.5-1.0	-	<2.0	-	-
Endocrine and Metabolic							
Gout	-	-	-	-	1.0	-	-
Gynecomastia	✔	0.5-1.5	-	-	-	-	-
Hyperglycemia	1.0	-	-	-	-	-	-
Thirst	1.0	-	-	-	-	-	-
Gastrointestinal							
Abdominal discomfort	-	-	0.0-5.1	-	<2.0	-	-
Abdominal pain	1.6	0.5-1.5	0.7*	-	<3.0	-	-
Acid regurgitation	-	0.5-1.5	-	-	-	-	-
Anorexia	1.0	-	-	-	-	-	1.0
Colitis	-	-	-	-	-	-	1.0
Constipation	1.0	0.3-1.5	1.2-3.8	0.6	3.3	-	-
Diarrhea	-	0.5-1.5	0.0-3.4	-	<2.0	1.7-4.2	-
Dry mouth	-	0.5-1.5	0.5-1.0	0.4-1.4	<3.0	-	-
Dyspepsia	-	0.5-3.9	-	0.8-1.5	<3-11	-	-
Dysphagia	1.0	-	-	-	-	-	1.0
Flatulence	1.0	0.5-1.5	-	-	<2.0	-	1.0
Gastritis	-	-	-	-	-	-	1.0
Gastrointestinal hemorrhage	-	-	-	-	-	1.0	1.0
Gastrointestinal symptoms	-	-	-	-	-	0.0-2.4	-
Hepatitis	-	-	-	-	-	1.0	1.0
Increased appetite	-	-	0.5-1.0	-	-	-	1.0
Jaundice	✔	-	-	-	-	1.0	-
Loose stools	1.0	-	-	-	-	-	-
Nausea	2.9	1.0-1.7	1.0-5.1	1.9-4.9	3.3-11	0.6-1.4	2.0
Pancreatitis	1.0	-	-	-	-	-	-
Vomiting	-	0.5-1.5	0.0-1.3	0.4-4.9	-	-	-
Genitourinary							
Decreased libido	-	-	0.5-1.0	-	-	-	-
Dysuria	-	0.5-1.5	0.5-1.0	-	1.0	-	-
Hematuria	-	-	-	0.7*	1.0	-	-

Adverse Event(s)	Amlod-ipine	Felod-ipine	Israd-ipine	Nicard-ipine	Nifed-ipine	Nimod-ipine	Nisold-ipine
Impotence	-	0.5-1.5	0.5-1.0	✔	<3.0	-	-
Micturition disorder	1.0	-	-	-	-	-	-
Nocturia	1.0	-	0.5-1.0	-	1.0	-	-
Pollakiuria	-	-	1.3-3.4	-	-	-	-
Polyuria	-	0.5-1.5	-	1.4*	0.5-3.0	-	-
Sexual dysfunction	1.0	-	-	-	<2.0	-	-
Urinary frequency/urgency	1.0	0.5-1.5	-	-	-	-	-
Hematological							
Anemia	-	0.5-1.5	-	-	0.5	1.0	-
Leukopenia	-	-	0.5-1.0	-	-	-	-
Purpura	1.0	-	-	-	-	-	-
Thrombocytopenia	1.0	-	-	✔	-	1.0	-
Laboratory Abnormalities							
Hepatic enzyme elevations	✔	0.5-1.5	0.5-1.0	✔	-	0.4-1.2	-
Hypokalemia	-	-	0.7*	-	-	-	-
Hyponatremia	-	-	-	-	-	1.0	-
Musculoskeletal							
Arthralgia	-	0.5-1.5	-	✔	<3.0	-	-
Arthrosis	1.0	-	-	-	-	-	-
Back pain	1.0	0.5-1.5	0.5-1.0	-	1.0	-	-
Hypertonia	-	-	-	✔	1.0	-	-
Inflammation	-	-	-	-	<2.0	-	-
Joint sprain	-	0.5-1.5	0.5-1.0	-	-	-	-
Muscle cramps	1.0	0.5-1.5	0.5-1.0	-	<3-8.0	0.0-1.4	-
Muscle weakness	-	-	0.0-1.2	-	10-12	-	-
Musculoskeletal chest pain	-	0.5-1.5	1.7-2.5	0.7*	<3.0	-	-
Myalgia	1.0	0.5-1.5	-	1.0	1.0	-	-
Neck pain	-	-	0.5-1.0	✔	-	-	-
Rhabdomyolysis	✔	-	-	-	-	-	-
Stiffness	-	-	-	-	<2.0	-	-
Twitching	1.0	-	-	-	-	-	-
Respiratory							
Bronchitis	-	0.5-1.5	-	-	-	-	-
Cough	-	0.8-1.7	0.5-1.0	-	1-6.0	-	-
Dyspnea	-	0.5-1.5	0.5-3.4	0.6-0.7	<3-6.0	0.0-1.2	-
Epistaxis	1.0	0.5-1.5	-	-	1.0	-	-
Influenza/flu-like illness	-	0.5-1.5	-	-	-	-	1.0
Nasal congestion	-	0.2-1.6	0.5-1.0	✔	<2-6.0	-	-
Shortness of breath	-	-	0.5-1.0	-	<2.0	1.0	-
Sinusitis	-	0.5-1.5	-	✔	1.0	-	3.0
Sore throat	-	-	-	✔	6.0	-	-
Upper respiratory tract infection	-	0.7-3.9	-	-	1.0	-	-
Other							
Abnormal visual accommodation	-	-	-	✔	1.0	-	-
Allergic reaction	1.0	-	-	✔	-	-	-
Angioedema	1.0	0.5-1.5	-	-	-	-	-
Balance difficulties	-	-	-	-	<2.0	-	-
Blurred vision	-	-	-	✔	<2.0	-	-
Breast pain	-	-	-	-	1.0	-	-
Cellulitis	-	-	-	-	-	-	1.0
Chills	-	-	-	-	<2.0	-	1.0
Conjunctivitis	1.0	-	-	✔	-	-	-

Adverse Event(s)	Amlod-ipine	Felod-ipine	Israd-ipine	Nicard-ipine	Nifed-ipine	Nimod-ipine	Nisold-ipine
Contusion	-	0.5-1.5	-	-	-	-	-
Decreased libido	-	0.5-1.5	-	-	-	-	-
Diplopia	1.0	-	-	-	-	-	-
Drowsiness	-	-	0.5-1.0	-	-	-	-
Ear pain/disorder	-	-	-	✔	-	-	-
Edema	1.8-10.8	-	3.5-35.9	0.6-1.0	-	0.4-1.2	-
Eye pain	1.0	-	-	-	-	-	-
Facial edema	-	-	-	-	-	-	1.0
Fatigue	4.5	-	2.5-8.5	-	5.9	-	-
Fever	-	-	0.5-1.0	✔ *	<2.0	-	1.0
Gingival hyperplasia	1.0	0.5-1.5	-	-	-	-	1.0
Glossitis	-	-	-	-	-	-	1.0
Hematoma	-	-	-	-	-	1.0	-
Hot flush	1.0	-	-	✔	-	-	-
Infection	-	-	-	✔	-	-	-
Injection site reaction/pain	-	-	-	1.4/0.7	-	-	-
Malaise	1.0	-	-	0.6	1.0	-	1.0
Nasopharyngitis	-	0.5-1.5	-	-	-	-	-
Numbness	-	-	0.5-1.0	-	-	-	-
Pain	1.0	-	-	0.6	<3.0	-	-
Parosmia	1.0	-	-	-	-	-	-
Pedal edema	-	-	-	5.9-8.0	-	-	-
Peripheral edema	18-26.0	2.0-17.4	-	✔	7-10.0	-	22.0
Pharyngitis	-	-	-	-	-	-	5.0
Pharyngolaryngeal pain	-	-	0.5-1.0	-	-	-	-
Rigors	1.0	-	-	-	1.0	-	-
Taste perversion	-	-	-	-	1.0	-	-
Tinnitus	1.0	-	-	✔	<5.0	-	-
Visual disturbance	-	0.5-1.5	0.5-1.0	-	<5.0	-	-
Warm sensation	-	0.9-1.5	-	-	-	-	-
Weight gain	1.0	-	0.5-1.0	-	1.0	-	-
Weight loss	1.0	-	-	-	-	-	-
Xerophthalmia	1.0	-	-	-	-	-	-

*IV formulation only.
✔ Percent not specified.
- Event not reported or incidence <1%.

Table 7. Black Box Warning for Nimodipine[41]

WARNING
Do not administer nimodipine intravenously or by other parenteral routes. Deaths and serious, life threatening adverse events have occurred when the contents of nimodipine capsules have been injected parenterally (See WARNINGS and DOSAGE AND ADMINISTRATION).

VII. Dosing and Administration

The usual dosing regimens for the single entity dihydropyridines are summarized in Table 8.

Table 8. Usual Dosing for the Single Entity Dihydropyridines [29-42]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amlodipine	Chronic Stable or Vasospastic Angina: Tablet: maintenance, 5 to 10 mg daily; maximum, 10 mg daily	Age 6 to 17 years Hypertension: Initial: 2.5 mg daily;	Tablet: 2.5 mg 5 mg

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertension: Tablet: initial, 5 mg daily; maintenance, 5 to 10 mg daily; maximum, 10 mg daily	maintenance 2.5 to 5 mg daily; maximum 5 mg daily	10 mg
Felodipine	Hypertension: Tablet: maintenance, 5 mg daily; range 2.5 to 10 mg daily	Safety and efficacy has not been established in pediatric patients.	Tablet: 2.5 mg 5 mg 10 mg
Isradipine	Hypertension: Tablet: initial, 2.5 mg twice daily; maintenance, 2.5 to 10 mg daily; maximum, 20 mg daily Tablet CR: initial, 5 mg daily; maintenance, 5 to 10 mg daily; maximum, 20 mg daily	Safety and efficacy has not been established in pediatric patients.	Tablet: 2.5 mg 5 mg Tablet Controlled Release (CR): 5 mg 10 mg
Nicardipine	Chronic Stable Angina Capsule: initial, 20 mg three times daily; maintenance, 20 to 40 mg three times daily Hypertension: Capsule: initial, 20 mg three times daily; maintenance, 20 to 40 mg three times daily Capsule SR: initial, 30 mg twice daily; maintenance, 30 to 60 mg twice daily Intravenous: short term, slow continuous infusion 0.1 mg/mL; initial, 50 mL/hour (5.0 mg/hour); maximum, 150 mL/hour (1.50 mg/hour); dosage must be individualized	Safety and efficacy has not been established in pediatric patients.	Capsule: 20 mg 30 mg Capsule Sustained Release (SR): 30 mg 45 mg 60 mg Ampules: 2.5 mg/mL
Nifedipine	Chronic Stable Angina Capsule: initial, 10 mg three times daily; maintenance, 10 to 20 mg three times daily; maximum, 180 mg daily Capsule ER: initial, 30 or 60 mg daily; maintenance, 30 to 90 mg; maximum, 120 mg daily Hypertension Capsule ER: initial, 30 or 60 mg daily; maintenance, 30 to 90 mg; maximum, 120 mg daily Vasospastic Angina Capsule: initial, 10 mg three times daily; maintenance, 20 to 30 mg three to four times daily; maximum, 180 mg daily Capsule ER: initial, 30 or 60 mg daily; maintenance, 30 to 90 mg; maximum, 120 mg daily	Safety and efficacy has not been established in pediatric patients.	Capsule: 10 mg 20 mg Tablet Sustained Release (CC, CR, XL, ER): 30 mg 60 mg 90 mg
Nimodipine	Subarachnoid hemorrhage Capsule: 60 mg every 4 hours for 21 consecutive days	Safety and efficacy has not been established in pediatric patients.	Capsule: 30 mg
Nisoldipine	Hypertension	Safety and efficacy has	Tablet Sustained

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet (new formulation): initial , 17 mg once daily; maintenance, 17 to 34 mg daily; maximum, 34 mg daily Tablet (old/ to be discontinued formulation): initial , 20 mg once daily; maintenance, 20 to 40 mg daily; maximum, 60 mg daily	not been established in pediatric patients.	Release (new formulation): 8.5 mg 17 mg 25.5 mg 34 mg Tablet Sustained Release (old/ to be discontinued formulation): 10 mg 20 mg 30 mg 40 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity dihydropyridine calcium-channel blocking agents are summarized in Table 9.

Table 9. Comparative Clinical Trials for the Single Entity Dihydropyridines

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Angina				
Koenig et al[51] Amlodipine 5 to 10 mg QD vs felodipine ER 5 to 10 mg QD	DB, PRO, RCT, XO Patients, age 30 to 80 years, who have a history of angina, a positive exercise-stress test or positive 24-hour ambulatory monitoring, and ≥ 6 ischemic episodes in 24 hours	N=52 8 weeks (4 weeks of each treatment)	Primary: Number of ST-segment depressions in 24 hours of ambulatory monitoring Secondary: Total and mean duration of each ST-segment depression episode, maximum ST depression, length of ischemic episode, adverse events	Primary: Significant reductions from baseline were seen in both groups for the number of ST-segment depressions, from 19.9 at baseline for both groups to 2.3 for amlodipine and 2.4 for felodipine (P<0.001 for both from baseline; P=0.83 between treatments). Secondary: Total and mean duration of each ST-segment depression episode, maximum ST depression and length of ischemic episode were significantly different from baseline for both treatment groups but treatments were not significantly different (P<0.001 for all from baseline, P=0.53, 0.40, 0.68, 0.35 respectively between treatments). Adverse event rates similar between the treatments (P value not reported).
Hypertension				
Sheehy et al[52] Amlodipine QD, initial dose 2.5 to 10 mg QD vs felodipine QD, initial dose 2.5 to 10 mg QD	RETRO Patients, age 65 years and older, with hypertension	N=7,818 (5,818 amlodipine, 2,630 felodipine)	Primary: Prescription renewal, drug switch rates, compliance rates, office visits Secondary: Not reported	Primary: Patients prescribed amlodipine had a greater compliance rate, 67.9%, than those prescribed felodipine 66.2% (P<0.01). Discontinuation rates were higher in the felodipine group by 27%. Amlodipine treatment resulted in more continuous months of treatment (69.2), than felodipine treatment (57.8) (P<0.01). Renewal rates were significantly larger in the amlodipine group (89.0%), than the felodipine group (85.6%) (P<0.01). Switch rates were significantly larger, 5 times, in the felodipine

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				group (10.2%) than the amlodipine group (1.9%) (*P*<0.01). Visits to specialists occurred significantly more in patients treated with amlodipine than felodipine, (OR, 1.14; 95% CI, 1.08 to 1.20).
Van der Krogt et al[53] Amlodipine 5 to 10 mg QD vs felodipine ER 5 to 10 mg QD	DB, MC, PG, RCT Patients, age 18-75 years old, with mild to moderate hypertension (DBP ≥95 mm Hg and ≤114 mm Hg)	N=201 12 weeks	Primary: Number of responders (DBP ≤90 mm Hg after 12 weeks of monotherapy or decrease of >10 mm Hg if baseline DBP >100 mm Hg) who did not experience serious adverse events Secondary: Blood pressure, adverse events	Primary: Amlodipine treatment resulted in significantly more responders than felodipine treatment (*P*=0.046). 68% (69 of 101) of the amlodipine group were responders. 53% (49 of 92) of the felodipine group were responders. 32% (32 of 101) of the amlodipine group were not responders. 47% (43 of 92) of the felodipine group were not responders. Secondary: The decreases in SBP and DBP from baseline were significant within each group but similar between the groups (amlodipine SBP and DBP 12 weeks vs baseline; *P*<0.001, felodipine SBP and DBP 12 weeks vs baseline; *P*<0.001, amlodipine 12 week change vs felodipine 12 week change; *P*>0.05). Adverse events were experienced by 33% of the amlodipine group and 42% of the felodipine group. Significantly more patients in the felodipine group experienced serious adverse events (9 patients who experienced 17 serious events vs 2 patients who experienced 3 serious events; *P*=0.048).
Mounier-Vehier et al[54] Amlodipine 5 mg QD vs nicardipine 60 mg/daily, divided 2 to 3 times daily	DB, MC, PG RCT Men and women, age 60 years and older with isolated systolic hypertension (SBP= 160-208 mm Hg) and DBP <90 mm Hg	N=133 90 days	Primary: Mean difference in SBP from baseline to day 90 Secondary: Mean difference in DBP, pulse pressure, heart rate, percent of patients with normal blood pressure	Primary: The decrease in SBP from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline; *P*=0.0001, nicardipine day 90 vs baseline; *P*=0.0001, amlodipine 90 day change vs nicardipine 90 day change; *P*=0.38). Secondary: The decrease in DBP from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline; *P*=0.0001; nicardipine day 90 vs baseline; *P*=0.0003,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			(<140/90 mm Hg), safety	amlodipine 90 day change vs nicardipine 90 day change; *P*=0.12). The decrease in pulse pressure from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline, *P*=0.0001; nicardipine day 90 vs baseline, *P*=0.0001; amlodipine 90 day change vs nicardipine 90 day change, *P*=0.88). There was no difference between the groups in heart rate (*P*=0.60). At day 90, 25.9% and 23.4% of the amlodipine and nicardipine groups had achieved normal blood pressure (*P*=0.76). The numbers of people in each group reporting at least 1 adverse event were similar, 23 in the amlodipine group and 20 in the nicardipine group (*P* value not reported).
Kes et al[55] Amlodipine 5 to 10 mg QD vs nifedipine 30 to 60 mg QD	MC, OL, RCT Patients with hypertension	N=155 12 weeks	Primary: Change in DBP Secondary: Not reported	Primary: There was no significant difference in DBP between the amlodipine group and nifedipine group at 12 weeks (*P*=0.436). Secondary: Not reported
Ryuzaki et al[56] i-TECHO Amlodipine 2.5 to 10 mg QD vs nifedipine CR 20 to 80 mg QD	OL, RCT, XO Patients treated for hypertension (SBP >140 mm Hg or DBP >90 mm HG)	N=55 12 weeks (6 weeks per treatment)	Primary: Average home blood pressure readings, pulse rates, clinic blood pressure and pulse readings Secondary: Not reported	Primary: The morning home SBP and DBP readings were lower in the nifedipine group than the amlodipine group (SBP 131±8 vs 133±10 mm Hg; *P*<0.05, DBP 80±8 vs 81±8 mm Hg; *P*<0.05). There were no significant differences in evening home blood pressure readings (*P*>0.05). There was no significant difference in rates of achieving target blood pressure between the groups (*P*<0.05). Morning home pulse rates were greater in the nifedipine group than the amlodipine group (70±9 vs 69±9 beats/min; *P*<0.05).

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				There were no significant differences between the groups in evening home pulse rates (*P*>0.05). The clinic SBP and DBP readings were significantly lower in the nifedipine group than in the amlodipine group (*P*<0.05). There were no significant differences between the groups in clinic pulse rates (*P*>0.05).
Gustin et al[57] Felodipine 5 to 10 mg QD vs nifedipine 30 to 60 mg QD	XO Patients with hypertension, stable on nifedipine for at least 3 months were switched to felodipine	N=127 2 months	Primary: Blood pressure Secondary: Side effects and use of supplemental antihypertensive agents	Primary: There was no difference in SBP before and after switching agents. However, there was a difference in DBP, which was slightly lower (–2±2 mm Hg) with felodipine than with nifedipine treatment (*P*<0.05). Secondary: Reported adverse events by patients and providers did not differ between the agents, with the most commonly reported side effect for both groups being leg swelling/edema. There was no difference in use of supplemental antihypertensive agents and heart rate between treatments (*P*>0.05 for both).
Saito et al[58] ADVANCE-Combi Amlodipine 2.5 to 5 mg QD vs nifedipine CR 20 to 40 mg QD Valsartan 40 to 80 mg daily was added on if blood pressure goal not met.	DB, RCT Patients with untreated essential hypertension with sitting SBP ≥160 mm Hg or DBP ≥100 mm Hg; or previously treated with sitting SBP ≥150 mmHg or DBP ≥95 mm Hg	N=514 16 weeks	Primary: Target blood pressure, achievement rate Secondary: Safety	Primary: Target blood pressure achievement rates were higher for the nifedipine treatment group than the amlodipine group (*P*<0.001). Patients in the amlodipine group were more likely to require additional treatment with valsartan or a dose increase of amlodipine (*P*<0.05). The reduction in blood pressure from baseline was greater in the nifedipine group (-34.0/-20.1) than in the amlodipine group (-27.0/-15.9; *P*<0.05). Secondary: Adverse event rates were not significantly different between the groups, 12.4% in the nifedipine group vs 7.6% of the amlodipine group (*P*=0.07).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Pepine et al[59] CESNA-II Amlodipine 5 to 10 mg QD vs nisoldipine ER 20 to 40 mg QD	DB, DD, PG, MC, RCT Men and women with hypertension (DBP 90-109 mm Hg) and coronary artery disease	N=not specified 6 weeks	Primary: Change from baseline in DBP at 6 weeks Secondary: Exercise duration, antihypertensive responder rate (% of patients with DBP <90 mm Hg), exercise test responder rate (increase in time by 20% and 60 seconds)	Primary: At 6 weeks, the mean SBP and mean DBP for the 2 treatment groups were not significantly different from each other and mean reductions in blood pressure were similar: amlodipine SBP/DBP 138/83 mm Hg, a decrease of 13/11 mm Hg, vs nisoldipine 137/81 mm Hg, a decrease of 15/13 mm Hg) (all *P* values not significant). Secondary: Both treatment groups experienced increases in exercise duration, increased by 21 seconds in the amlodipine group and 23 seconds in the nisoldipine group (*P*=0.268). Antihypertensive and exercise responder rates were similar between the groups (antihypertensive rates: 78% for amlodipine and 87% for nisoldipine; *P*>0.05 for both).
Whitcomb et al[60] Amlodipine 2.5 to 10 mg QD vs nisoldipine ER 10 to 40 mg QD	DB, DD, MC, RCT Men and women, age 21 to 75 years, with hypertension	N=161 8 weeks	Primary: Between treatment comparison of change from baseline in DBP Secondary: Change from baseline in SBP, heart rate, percent of patients who responded	Primary: Treatment with amlodipine resulted in a significantly larger change from baseline, between-group difference of 2.7 mm Hg; *P*=0.005. However, a pre-specified difference of greater than 5 mm Hg in least mean squares, here 1.1 to 4.3 mm Hg, showed that the treatments were similar in reduction of DBP. Secondary: Amlodipine treatment resulted in a significantly larger change from baseline in SBP than nisoldipine treatment (*P* value not reported, least mean square difference >5 mm Hg). At week 8, more patients in the amlodipine group were responders, 79%, as compared to the nisoldipine group, 60% (*P*=0.004).
White et al[61] CESNA-III	DB, MC, PRO, RCT African American	N=192 12 weeks	Primary: ABPM change from baseline in DBP in mean 24 hour period	Primary: The decrease from baseline in DBP was similar between the groups: –16.0±2.3 mm Hg for nisoldipine and – 15.0±2.3 mm Hg for amlodipine (*P*=0.500).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Amlodipine 5 to 10 mg QD vs nisoldipine ER 20 to 60 mg QD	patients with hypertension (blood pressure of 92 mm Hg to 114 mm Hg and SBP <200 mm Hg)		Secondary: ABPM change in SBP, awake and asleep blood pressure, changes in clinic blood pressure and pulse	Secondary: The decrease from baseline in SBP was similar between the groups: –23.0±2.7 mm Hg for nisoldipine and –19.9±2.7 mm Hg for amlodipine (*P*=0.067). The changes from baseline in awake and asleep SBP and DBP were not significantly different between the groups except for awake SBP, for which the nisoldipine group had a larger reduction, –19.2 vs –15.9 mm Hg (*P*=0.045). The changes from baseline in clinic blood pressure and pulse were similar between the groups (*P*>0.05 for SBP and DBP; *P*=0.362).
Lenz et al[62] Amlodipine 5 to 10 mg QD vs nisoldipine 10 to 20 mg QD	OL, XO Patients, 35 to 70 years old, with hypertension, (SBP 140-179 mm Hg and DBP 90-109 mm Hg), stable on amlodipine for at least 3 months prior to switch to nisoldipine	N=21 10 weeks	Primary: 24-hour ABPM Secondary: Not reported	Primary: No significant difference in ABPM was found after patients switched from amlodipine to nisoldipine for the following: systolic nighttime, daytime and 24-hour blood pressure, diastolic nighttime and daytime blood pressure (*P*>0.05 for all). 24-hour DBP was significantly lower with amlodipine treatment than with nisoldipine treatment (75±10 vs 77v8.5 mm Hg; *P*=0.017). Secondary: Not reported
Fogari et al[63] CANDIA Amlodipine 10 mg once QD vs candesartan cilexetil 16 mg and HCTZ 12.5 mg QD (separate entities)	DB, MC, RCT Patients, 20 to 80 years old, with mild to moderate uncomplicated hypertension not controlled on monotherapy with an antihypertensive (agents not listed),	N=203 8 weeks	Primary: Decrease in DBP Secondary: Sitting SBP, reduction of the orthostatic blood pressure at least two minutes after standing, change in heart rate, percentage of patients normalized (DBP <90	Primary: There was no significant difference in the mean decrease in DBP between treatment groups; the difference in final DBP was -0.02 mm Hg (95% CI, -1.48 to 1.52 mm Hg; *P*=0.979). Secondary: There was no significant difference between the groups at week 8 for the following: sitting SBP (*P*=0.835), heart rate (*P*<0.500), orthostatic SBP (*P*=0.883), orthostatic DBP (*P*=0.264), percentage of patients normalized (*P*=1.00), percentage of responders (*P*=0.900).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	(SBP <180 mg Hg and DBP 90 to 110 mg Hg)		mm Hg and SBP <140 mm Hg), percentage of responders (reduction in DBP >/= 5 mm Hg)	The number of patients reporting an adverse event was greater in the amlodipine group (*P*=0.001). The number of patients reporting an adverse drug-related event was greater in the amlodipine group (*P*<0.001). Changes in blood chemistry and other secondary measurements were not significantly different between the treatment groups.
Ogihara et al[64] CASE-J Amlodipine 2.5 to 10 mg QD vs candesartan 4 to 12 mg QD	AC, MC, OL, PG, PRO, RCT Patients with high risk hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg in patients < 70 years old <u>or</u> SBP ≥160 mm Hg or DBP ≥90 mm Hg in patients ≥ 70 years old), with either type 2 diabetes, history of stroke or ischemic attack, left ventricular hypertrophy, proteinuria or serum creatinine ≥1.3 mg/dL	N=4,703 Up to 4 years	Primary: First fatal/nonfatal cardiovascular event (composite of sudden death, cerebrovascular events, cardiac events including heart failure, angina pectoris, acute myocardial infarction, renal events, including serum creatinine increases, vascular events, including dissecting aortic aneurysm or arteriosclerotic occlusion Secondary: All-cause death, new-onset diabetes, discontinuation due to adverse events	Primary: 134 patients experienced a cardiovascular event in each treatment regimen (HR, 1.00; 95% CI, 0.78 to 1.27; *P*=0.969). Secondary: All-cause death rates did not differ between treatments, 73 deaths in the candesartan group and 86 in the amlodipine group (*P* value not reported). New-onset diabetes occurred in significantly fewer patients in the candesartan group than the amlodipine group (HR, 0.64; 95% CI, 0.43 to 0.97; *P*=0.033). 125 (5.4%) patients in the candesartan group and 134 (5.8%) of patients in the amlodipine group discontinued due to adverse events (*P* value not reported).
Ribeiro et al[65] LAMHYST Amlodipine 5 mg QD (option	DB, DD, PG, PRO, RCT Flexible-dose escalation study	N=194 12 weeks, with 2 days placebo treatment,	Primary: Difference between treatment groups in mean change in ABPM for last 9 hours of	Primary: After 12 weeks, mean reductions in SBP were significantly larger in the amlodipine group than the losartan group (–18.1 vs –10.1 mm Hg; *P*<0.001). Mean reductions in DBP were significantly larger in the amlodipine group than the losartan

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
to increase to 10 mg at 6 weeks) vs losartan 50 mg QD (option to increase to 100 mg at 6 weeks)	Males and females, age 18-79 years old, with diagnosis of mild (>95 mm Hg but <115 mm Hg) to moderate essential hypertension and not taking an antihypertensive medication (within last 4 weeks)	mimicking a drug holiday after 12 weeks on treatment	treatment and during drug holiday Secondary: Not reported	group (–18.1 vs –10.1 mm Hg; *P*<0.05). Mean increases in SBP were similar between the groups during the 2-day drug holiday (*P*>0.05). After the 2-day drug holiday, SBP was lower than baseline in both groups (P<0.001), with the amlodipine group SBP remaining significantly lower (*P*<0.01). Mean increases in DBP were similar between the groups during the 2-day drug holiday (*P*>0.05). After the 2-day drug holiday, DBP was lower than baseline in both groups (*P*=0.0001), with the amlodipine group DBP remaining significantly lower (*P*<0.05). Secondary: Not reported
Chrysant et al[66] Amlodipine 5 or 10 mg QD vs olmesartan 10, 20 or 40 mg QD vs Each possible combination of above amlodipine doses with above olmesartan doses: 5/10, 5/20, 5/40, 10/10, 10/20, 10/40 vs placebo	DB, factorial, MC, PC, RCT Patients, age 18 years and older, with seated DBP of 95 to 120 mm Hg	N=1,940 8 weeks	Primary: Change from baseline in seated DBP at week 8 Secondary: Change from baseline in seated SBP at week 8, mean change from baseline in seated DBP and SBP at weeks 2, 4, 6 and 8 without last observation carried forward, proportion of patients achieving BP goal (<140/90 mm Hg or <130/80 mm Hg), safety	Primary: All active treatments and placebo resulted in significant decreases in seated DBP at week 8 (*P*<0.001). Reductions in seated DBP with monotherapy treatment ranged from –8.3 to –12.7 mm Hg; reductions with combination therapy ranged from –13.8 to –19.0 mm Hg. All combinations reduced seated DBP significantly greater than either component as monotherapy at the same dosage (*P*<0.001). Secondary: All active treatments and placebo resulted in significant decreases in seated SBP at week 8 (*P*<0.001 for treatment, *P*=0.024 for placebo). All combinations reduced seated SBP significantly greater either component as monotherapy at the same dosage (*P*<0.001). The proportion of patients achieving goal BP were: 20.0% to 36.3% of patients receiving olmesartan monotherapy 21.1% to 32.5% of patients receiving amlodipine monotherapy 35.0% to 53.2% of patients receiving combination therapy

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				8.8% of patients receiving placebo. Combination therapy resulted in significantly greater achievement of goal BP than monotherapy (*P*<0.005). No difference in overall rates of adverse events across the different treatment groups was seen. 26.9% of patients experienced a drug-related adverse event. Changes in laboratory values were not considered clinically significant nor followed a consistent pattern with treatment: none of the changes were considered clinically significant. Platelet counts increased significantly from baseline (statistically) for patients receiving amlodipine, however the increase was <10% and not deemed clinically relevant.
Maciejewski et al[67] Amlodipine 5 to 10 mg QD (depending on response) vs valsartan 80 to 160 mg QD (depending on response) For all patients: if blood pressure exceeded 140/90 while on highest treatment dose, HCTZ 12.5mg/day was added to the regimen.	DB, PRO, RCT, XO African-Americans, older than 35 years, with baseline blood pressure >140/90 mm Hg and not on antihypertensive treatment	N=20 8-10 weeks for each arm with 2 week washout period before crossover	Primary: Comparison of 24 hour ABPM recordings Secondary: Magnitude of change from baseline in SBP and DBP with each treatment, percent of patients who achieved goal <140/<90 with each treatment based on clinic blood pressure measurements	Primary: There was no difference between the groups based on 24 hour ABPM: SBP amlodipine 130±8 vs valsartan 127±17 (*P*=0.350) and DBP amlodipine 82±5 vs valsartan 84±16 (*P*=0.430). Secondary: There was no difference between groups in magnitude of change from baseline in blood pressure (amlodipine -25±8/-18±7 vs valsartan -25±9/-16±7; *P*=0.61), and in percent of patients achieving goal blood pressure, 70% in the valsartan group and 75% in the amlodipine group (*P*=0.62).
Ichihara et al[68] Amlodipine 2.5 to 10 mg QD vs valsartan 40 to 160 mg QD	Patients with untreated hypertension (clinic SBP >140 mm Hg and/or DBP >90 mm Hg; or ABPM SBP >135 mm Hg	N=100 12 months	Primary: ABPM and clinic blood pressure Secondary: Pulse wave velocity, carotid intima-media	Primary: Both treatments resulted in significant decreases in blood pressure, both ambulatory and clinic, over 12 months from baseline; blood pressure decreases were similar between treatment groups (Between treatments: clinic SBP *P*=0.34; clinic DBP *P*=0.85; 24 hour ABPM *P*=0.14).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	and/or DBP >98 mm Hg)		thickness, urinary albumin excretion	Blood pressure variability decreased significantly in the amlodipine group compared to the valsartan group, where there was no change in blood pressure variability (*P*<0.01). Secondary: The decrease in pulse wave velocity was significant from baseline for both groups, but not significantly different from each other (*P*<0.05 from baseline). Intima-media thickness was not changed significantly from baseline for either treatment (*P*>0.05 for both from baseline). Urinary albumin excretion in the valsartan group decreased significantly both from baseline and compared to amlodipine treatment (*P*<0.05 from baseline, *P* value for comparison not reported).
Tatti et al[69] FACET Amlodipine 10 mg QD vs fosinopril 20 mg QD If blood pressure was not controlled on monotherapy, the other study drug was added.	OL, PRO, RCT Men and women, diagnosed with hypertension (SBP >140 mm Hg or DBP >90 mm Hg) and non-insulin dependent diabetes	N=380 Up to 3.5 years	Primary: Blood pressure Secondary: Fasting serum glucose, serum creatinine, plasma insulin, $HbA1_c$, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fibrinogen, microalbuminuria	Primary: Both treatment groups significantly lowered SBP and DBP from baseline (*P*<0.05). SBP was lower in the amlodipine group by 4 mm Hg than in the fosinopril group (*P*<0.01). There was no difference in DBP, both groups decreased by 8 mm Hg. Amlodipine was added by 30.7% of the fosinopril group and fosinopril was added by 26.2% of the amlodipine group (*P*>0.1). Secondary: No difference between the groups was found for serum creatinine, $HbA1_c$, and triglycerides at the endpoint (*P*>0.05). Fasting serum glucose, serum insulin and microalbuminuria were significantly lower at endpoint for both groups but not significantly different from each other (*P*>0.05). Total cholesterol increased in both groups, and high-density lipoprotein cholesterol increased significantly in the fosinopril

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				group (*P*<0.05). No difference in fibrinogen levels was observed between the groups at the end of the trial (*P*>0.05).
Cardiovascular Outcomes				
Pitt et al[70] PREVENT Amlodipine 5 to 10 mg QD vs placebo	DB, MC, PC, RCT Men and women, age 30 to 80 years with angiographic evidence of coronary artery disease, DBP <95 mm Hg, total cholesterol 325 mg/dL, fasting blood glucose <200 mg/dL	N=825 3 years	Primary: Change in mean minimal diameter with a quantitative coronary angiography Secondary: Progression of atherosclerosis in the carotid arteries assessed by B-mode ultrasonography for intimal-medial thicknesses, all-cause mortality, occurrence of major fatal/nonfatal vascular events or procedures, adverse events	Primary: Change, reduction, in the minimal diameter was similar between the amlodipine group and the placebo group (0.084 vs 0.0095 *P*=0.38). Secondary: Amlodipine treatment significantly decreased the progression of atherosclerosis as compared to placebo treatment, a 0.013 mm decrease for the amlodipine group vs a 0.033 mm increase with placebo (*P*=0.007). There was no difference in all-cause mortality between amlodipine and placebo. There was no difference in occurrence of fatal and nonfatal vascular events between the treatment groups (HR, 0.82; 95% CI, 0.47 to 1.42). Amlodipine treatment significantly reduced the occurrence of hospitalized congestive heart failure and unstable angina (HR, 0.65; 95% CI, 0.47 to 0.91) and coronary revascularizations (HR, 0.57; 95% CI, 0.41 to 0.81) and combined overall procedures (HR, 0.69; 95% CI, 0.52 to 0.92). There was no significant difference between groups in rates of adverse events: cancer rate (HR, 2.13; 95% CI, 0.90 to 5.21) and bleeding episode (HR, 1.42; 95% CI, 0.88 to 2.30).
Lichtlen et al[71] INTACT Nifedipine 80 mg QD	DB, MC, PC, PRO, RCT Patients, age 65 years and younger,	N=348 (282 without study deviations) 3 years	Primary: Progression of coronary artery disease detected on angiogram (change in minimal	Primary: In patients without study deviations, there were no significant differences in number of stenoses and occlusions per patient (nifedipine=3.7, placebo=3.88; *P*=0.437). The distribution among the arteries of the occlusions was not different between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo	demonstrating early coronary artery disease who were not candidates for invasive therapeutic procedures		diameter, percent stenosis, transition into occlusion, new stenosis) Secondary: Critical clinical events (cardiac death, nonfatal myocardial infarction, unstable angina, need for procedure, heart failure, severe arrhythmias), progression of new lesions	groups (*P* value not reported). The progression of stenosis was significant from baseline but changes were not significantly different between the groups (*P*<0.006 for all vs baseline; *P*>0.585 for group comparisons). Secondary: There was no difference between nifedipine treatment and placebo in number of critical events, 44 events in 24 patients receiving nifedipine vs 52 events in 35 patients in the placebo group (*P*=0.278). The nifedipine group had significantly fewer new lesions as compared to the placebo group: 78 (0.58 lesions/patients) vs 118 (0.8 lesions/patient) (*P*=0.031).
Borhani et al[72] MIDAS Isradipine 2.5 to 5 mg BID vs HCTZ 12.5 to 25 mg QD	DB, MC, positive-control, RCT Patients, average of 58.5 years old, with hypertension	N=883 3 years	Primary: Rate of progression of intimal-medial thickness in carotid arteries Secondary: Rate of cardiovascular events (myocardial infarction, stroke, congestive heart failure, angina, sudden death), rate of nonmajor cardiovascular events and procedures (transient ischemic attacks, dysrhythmia, aortic valve replacement, femoral popliteal bypass graft), blood pressure	Primary: There was no difference in the rate of progression of intimal-medial thickness between the treatment groups (*P*=0.68). Secondary: The rate of cardiovascular events was greater in the isradipine group than in the HCZT group (5.65% vs 3.17%; *P*=0.07). The rate of nonmajor cardiovascular events was greater in the isradipine group than in the HCTZ group (9.05% vs 5.22%; *P*=0.02). There was a significant decrease in SBP in the HCTZ group as compared to isradipine (-19.5 vs -16.0 mm Hg; *P*=0.002). There was no difference in change in DBP (both groups -13.0 mm Hg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
National Intervention Cooperative Study[73] NICS-EH Nicardipine SR 20 mg BID vs trichlormethiazide 2 mg QD	DB, RCT Patients age 60 years old and older with a SBP between 160 to 220 mm Hg and a DBP < 115 mm Hg and no history of cardiovascular complications	N=414 5 years	Primary: Cardiovascular complications Secondary: Blood pressure, pulse, side effects, laboratory values	Primary: There was no difference in rate of cardiovascular complications during the study period (*P*=0.923). There was no difference in the number of patients experiences left ventricular hypertrophy on electrocardiogram (*P*=0.975). Secondary: Both groups experienced significant reductions in blood pressure from baseline (*P*=0.000). There was no significant difference in pulse rate between the groups (*P* value not reported). Side-effect rates did not differ between the groups (*P*=0.897). More patients in the trichlormethiazide group than in the nicardipine group had abnormal lab results at the end of the study; differences were significant for serum sodium levels (decreased in the trichlormethiazide group) and uric acid levels (increased with trichlormethiazide).
Zanchetti et al[74] VALUE Amlodipine 5 mg QD (inital dose) vs valsartan 80 mg QD (initial)	DB, PG, RCT Patients with hypertension (subgroup analysis of VALUE trial)	N=15,245 4.2 years	Primary: Time to first cardiac event, analyzed by subgroup Secondary: Myocardial infarction, heart failure and stroke	Primary: The only significant result of the analyses by subgroup for time to first cardiac event was sex; women in the valsartan group experienced more cardiac events as compared to men in the valsartan group (HR for women, 1.21; 95% CI, 1.03 to 1.42; HR for men, 0.94; 95% CI, 0.82 to 1.07; *P*=0.016). The VALUE trial showed no difference in the primary outcome as well as in cardiac morbidity and mortality between amlodipine treatment and valsartan treatment. SBP and DBP were lower, as was incidence of myocardial infarction, in the amlodipine treatment group as compared to the valsartan group. Secondary: Male patients treated with valsartan had a significantly lower incidence of heart failure than males treated with amlodipine

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				(*P*<0.001 for male vs female difference; for men, HF rates with valsartan were 4.1% vs amlodipine 5.8% [HR, 0.73; 95% CI, 0.60 to 0.88]; for women, rates were valsartan 5.3% vs amlodipine 4.6%, [HR, 1.18; 95% CI, 0.95 to 1.47]). Patients without a history of stroke had a greater reduction in stroke risk if treated with amlodipine (valsartan 3.4% vs amlodipine 2.6%; HR, 1.34; 95% CI, 1.09 to 1.65).
Brown et al[75] INSIGHT Nifedipine 30 mg QD vs amiloride 2.5 mg and HCTZ 25 mg QD (combination product) Doses were doubled or atenolol 25 to 50 mg or enalapril 5 to 10 mg was added.	DB, MC, PRO, RCT Patients, age 55 to 80 years old with hypertension (blood pressure ≥150/95 mm Hg or SBP ≥160 mm Hg) and at least 1 cardiovascular risk factor	N=6,575 3 years	Primary: Composite death from any cardiovascular cause together with nonfatal stroke, myocardial infarction, or heart failure Secondary: Total mortality, death from a vascular cause, nonfatal vascular event	Primary: There was no difference in composite cardiovascular deaths between the groups. Events occurred in 200 (6.3%) patients in the nifedipine group and 182 (5.8%) of the amiloride/HCTZ group (18.2 vs 16.5 events per 1,000 patient-years; *P*=0.34). Secondary: There was no difference in all-cause mortality (*P*=0.62), death from a vascular cause (*P*=0.67) and in nonfatal vascular events (*P*=0.50) between the treatment groups.
Dahlöf et al[76] ASCOT-BPLA Amlodipine 5 to 10 mg QD (with option to add perindopril 4 to 8 mg QD as required) vs atenolol 50 to 100 mg QD (with option of adding	DB, MC, PRO, RCT Patients, age 40 to 79 years of age, with hypertension and at least 3 other cardiovascular risk factors	N=19,257 5.5 years	Primary: Nonfatal myocardial infarction and fatal coronary heart disease Secondary: All-cause mortality, total stroke, primary endpoint minus silent myocardial infarction, all coronary events, total cardiovascular events and procedures,	Primary: There was no significant difference in rates of nonfatal myocardial infarction and fatal coronary heart disease between amlodipine treatment and atenolol treatment (8.2 events per 1,000 patient-years vs 9.1 events per 1,000 patient-years (HR, 9.1; 95% CI, 0.79 to 1.02). Secondary: The amlodipine group had significant reductions in the following endpoints as compared to the atenolol group: nonfatal myocardial infarction (excluding silent myocardial infarction) and fatal coronary heart disease (*P*=0.0458), total coronary events (*P*=0.0070), total cardiovascular events and procedures

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
bendroflumethiazide 1.25 to 2.5 mg QD as required)			cardiovascular mortality, nonfatal and fatal heart impairment	(*P*<0.0001), all-cause mortality (*P*=0.0247), cardiovascular mortality (*P*=0.001), fatal and nonfatal stroke (*P*=0.0003).
Nissen et al[77] CAMELOT Amlodipine 10 mg QD vs enalapril 20 mg QD vs placebo	DB, MC, PC, RCT Men and women, age 30 to 79 years old who required coronary angiography for evaluation for chest pain or percutaneous coronary intervention, with a DBP <100 mm Hg, who had 1 or more lesion with greater than 20% stenosis on angiograph	N=1,997 24 months	Primary: Incidence of adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for congestive heart failure, stroke or transient ischemic attack, new diagnosis of peripheral vascular disease) Secondary: Incidence of adverse events and revascularization	Primary: Significantly fewer cardiovascular events occurred in the amlodipine group as compared to the placebo group (110 vs 151; HR, 0.69; 95% CI, 0.54 to 0.88; *P*=0.003). Rates of cardiovascular events were similar between the amlodipine treatment group and the enalapril treatment group (110 vs 136; HR, 0.81; 95% CI, 0.63 to 1.04; *P*=0.10). Rates of cardiovascular events were similar between the enalapril treatment group and the placebo treatment group (136 vs 151; HR, 0.85; 95% CI, 0.67 to 1.07; *P*=0.16). Secondary: The incidence of adverse events was not significantly different among treatment groups (*P* values not significant). No difference was found among all groups for the endpoint of all-cause mortality (*P* values not significant). The incidence of revascularization was significantly lower in the amlodipine group (4.1%) as compared to the placebo group (7.9%) (*P*=0.002). No significant difference was seen for amlodipine compared to enalapril, or enalapril compared to placebo (*P*=0.09 and *P*=0.17).
Estacio et al[78] ABCD Nisoldipine vs	DB, PRO, RCT Patients, age 40 to 74 years, with diabetes, with elevated blood pressure, (DBP >80 mm Hg)	N=470 67 months	Primary: Cardiovascular events Secondary: Not reported	Primary: Patients in the enalapril group had significantly fewer cardiovascular events than the nisoldipine group including nonfatal myocardial infarctions (*P* =0.001), all myocardial infarctions (*P* =0.001), and all cardiovascular events (*P*=0.002). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
enalapril vs. placebo Open-label add-on treatment of metoprolol or HCTZ was used if blood pressure goal was not achieved with study drug.				
ALLHAT Collaborative Research Group[79] ALLHAT Amlodipine 2.5 to 10 mg QD vs lisinopril 10 to 40 mg QD vs chlorthalidone 12.5 to 25 mg QD	AC, DB, MC, RCT Men and women, age 55 years old and older, with hypertension and at least 1 coronary heart disease risk factor	N=33,357 4.9 years (average follow-up)	Primary: Combined fatal coronary heart disease and nonfatal myocardial infarction Secondary: All-cause mortality, stroke, combined coronary heart disease, combined cardiovascular disease	Primary: No significant difference was observed between amlodipine and chlorthalidone in combined fatal coronary heart disease and nonfatal myocardial infarction (RR, 0.98; 95% CI, 0.90 to 1.07). No significant difference was observed between lisinopril and chlorthalidone in combined fatal coronary heart disease and nonfatal myocardial infarction (RR, 0.99; 95% CI, 0.91 to 1.08). Secondary: No significant difference was observed between amlodipine and chlorthalidone in all-cause mortality, combined coronary heart disease, stroke, combined cardiovascular disease, angina, coronary revascularization, and peripheral artery disease (P>0.05). The amlodipine group had a 38% greater risk of heart failure than chlorthalidone (P<0.001). No significant difference was observed between lisinopril and chlorthalidone in all-cause mortality, combined coronary heart disease and peripheral artery disease (P>0.05). The lisinopril group had a 15% greater risk of stroke than the chlorthalidone group (P=0.02), a 10% greater risk for combined cardiovascular disease (P<0.001), and an 11% greater risk for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				hospitalized/treated angina (*P*=0.01).
Black et al[80] ALLHAT Amlodipine 2.5 to 10 mg QD vs lisinopril 10 to 40 mg QD vs chlorthalidone 12.5 to 25 mg QD	MC, RCT Men and women, age 55 years old and older, with hypertension and metabolic syndrome, patients with diabetes were excluded	N=17,515 4.9 years	Primary: Fatal coronary heart disease and nonfatal myocardial infarction Secondary: All cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease	Primary: For patients with metabolic syndrome, there was no significant difference in rates of coronary heart disease and nonfatal myocardial infarction with amlodipine vs chlorthalidone (RR, 0.96; 95% CI, 0.79 to 1.16), or lisinopril vs chlorthalidone (RR, 1.05; 95% CI, 0.88 to 1.27). Secondary: For patients with metabolic syndrome, there were no significant differences found between amlodipine vs chlorthalidone in all secondary endpoints (*P* value not significant). For patients without metabolic syndrome, amlodipine treatment was associated with significantly more heart failure, but in patients with metabolic syndrome, there was no difference (*P*=0.03). Patients with metabolic syndrome who received lisinopril experienced more heart failure and cardiovascular disease than those who received chlorthalidone (RR, 1.31; 95% CI, 1.04 to 1.64 and RR, 1.19; 95% CI, 1.07 to 1.32).
Hansson et al[81] STOP-Hypertension Felodipine 2.5 mg or isradipine 2.5 mg QD vs enalapril 10 mg or lisinopril 10 mg QD vs atenolol 50 mg or metoprolol	MC, OL, PRO, RCT Men and women, age 70-84 years with hypertension (SBP ≥180mm Hg or DBP ≥105 mm Hg or both)	N=6,614 4 years	Primary: Fatal stroke, fatal myocardial infarction, other fatal cardiovascular events Secondary: Blood pressure	Primary: The rate of prevention of cardiovascular deaths was similar in all groups (RR, 0.97 to 1.04; 95% CI, 0.86 to 1.26). Fatal cardiovascular events, including fatal stroke and fatal myocardial infarction, occurred in 19.8 per 1,000 patient-years in the β-blocker and/or HCTZ group, in the felodipine or isradipine group and in the enalapril or lisinopril group (RR, 0.99; 95% CI, 0.84 to 1.16). The relative risk of cardiovascular death in patients in the enalapril or lisinopril group as compared to the felodipine or isradipine group was 1.04 (95% CI, 0.86 to 1.26; *P*=0.67.) Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
100 mg or pindolol 5 mg QD and /or HCTZ 25 mg with amiloride 2 to 5 mg QD				Decreases in blood pressure were similar among the groups.
Renal Effects				
Agodoa et al[82] AASK Amlodipine 5 to 10 mg QD vs ramipril 2.5 to 10 mg QD	DB, MC, RCT African American patients, age 18 to 70 years old, with hypertensive renal disease (GFR 20 to 65 mL/min)	N=1,094 4 years	Primary: Rate of change in GFR (GFR slope) Secondary: Composite of: confirmed reduction GFR by 50% or by 25 mL/min for baseline, end-stage renal disease	Primary: The average decline in GFR was slower, by 36% in the ramipril group as compared to the amlodipine group (*P*=0.002). However, during the first 3-months, GFR increased more in the amlodipine group than the ramipril group (*P*<0.001). The mean total slope did not differ between the groups (*P*=0.38). Secondary: The risk reduction for the composite secondary outcome was significantly greater for the ramipril group than the amlodipine group (*P*=0.005). Additionally, the rate of end-stage renal disease was significantly lower in the ramipril group (*P*=0.01).
Lewis et al[83] Amlodipine 2.5 to 10 mg QD vs irbesartan 75 to 300 mg QD vs placebo	DB, MC, PRO, RCT Patients, age 30 to 70 years, with a diagnosis of type 2 diabetes, hypertension, proteinuria and serum creatinine between 1.0 to 3.0 mg/dL in females or 1.2 to 3.0 mg/dL in males	N=1,715 3 years	Primary: Composite: twice the baseline serum creatinine, onset of end-stage renal disease, death Secondary: Composite: death from cardiovascular causes, nonfatal myocardial infarction, heart failure with hospitalization, cerebrovascular event leading to permanent neurologic damage, lower limb amputation	Primary: Patients in the irbesartan group had a significantly lower risk of achieving the composite primary endpoint as compared to the placebo group and to the amlodipine group (20% reduced vs placebo; *P*=0.03, 23% reduced risk vs amlodipine; *P*=0.006). The risk difference between amlodipine and placebo was not significant (*P*=0.47). Secondary: There was no significant difference found between the groups for composite cardiovascular outcomes: irbesartan vs placebo (*P*=0.40), amlodipine vs placebo (*P*=0.27), amlodipine vs irbesartan (*P*=0.78). Serum creatinine increased more slowly in the irbesartan group, as compared to the placebo group (24% slower; *P*=0.008), and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			above the ankle, serum creatinine	the amlodipine group (21% slower; *P*=0.02).
Wright et al[84] AASK Amlodipine 5 to 10 mg QD vs metoprolol 50 to 200 mg QD vs ramipril 2.5 to 10 mg QD	MC, RCT African American patients, age 18 to 70 years old, with hypertensive renal disease (GFR 20 to 65 ml./min)	N=1,094 4 years	Primary: Rate of change in GFR Secondary: Composite of: confirmed reduction in GFR by 50% or by 25 ml/min for baseline, end-stage renal disease, death	Primary: The mean GFR decline did not significantly differ between the usual and lower blood pressure groups for the chronic phase, after 3 months of treatment, or during the 4 year follow-up (*P*=0.33 and *P*=0.24). The mean GFR decline was slower in the ramipril treatment group than the in metoprolol group for the acute phase, first 3 months of treatment, and the 4 year follow-up (*P*=0.01 and *P*=0.007). The mean GFR decline was faster in the amlodipine treatment group than the in metoprolol group for the chronic phase, but GFR increased during the acute phase, and therefore GFR decline was slower at 3 year follow-up (*P*=0.02, *P*<0.001, *P*=0.004). Secondary: There was no significant difference in the risk of composite secondary outcome between the usual blood pressure group and the lower blood pressure group (*P*=0.85). There were no significant differences in the risk reduction of composite secondary outcome and end-stage renal disease between the ramipril group and the metoprolol group (*P*=0.04; *P* value not reported). There were no significant differences in the risk reduction of composite secondary outcome between the amlodipine group and the metoprolol group (*P*=0.17). The metoprolol group had significantly lower risk than the amlodipine group for end-stage renal disease or death (*P*=0.003, *P*<0.001).
Subarachnoid Hemorrhage				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Schmid-Elsaesser et al[85] Nimodipine continuous infusion of 1.0 mg/hour for 6 hours, followed by 2.0 mg/hour vs magnesium sulfate bolus infusion 10 mg/kg, followed by continuous infusion of 30 mg/kg QD	RCT Patients with aneurismal subarachnoid hemorrhage	N=104 7 days	Primary: Incidence of clinical vasospasm and transcranial doppler/angiographic vasospasm, and infarction attributable to vasospasm Secondary: Incidence of angiographic vasospasm	Primary: There was no significant difference between the groups in number of patients experiencing clinical vasospasm or transcranial doppler/angiographic vasospasm: 14 patients (27%) in the nimodipine group vs 8 patients (15%) in the magnesium group (*P*=0.193); 17 (33%) in the nimodipine group vs 20 (38%) in the magnesium group (*P*=0.792). No difference between the groups was found in incidence of cerebral infarction, 11 (22%) in the nimodipine group vs 10 (19%) in the magnesium group (*P* value not reported). Secondary: There were no significant differences in incidence of angiographic vasospasm, neuronal markers (*P* values not reported) or Glasgow outcome scores (all values: *P*>0.05).

Drug regimen abbreviations: BID=twice daily, CR=controlled release, ER=extended release, QD=once daily, SR=sustained release
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, XO=crossover
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, DBP=diastolic blood pressure, GFR=glomerular filtration rate, $HbA1_c$=hemoglobin $A1_c$, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
Lenz et al[62] compared the 24-hour blood pressure control in 25 patients stabilized on amlodipine who were then converted to nisoldipine. After 3 months, blood pressure control was similar between treatments, except for average 24-hour diastolic blood pressure, where nisoldipine treatment resulted in slightly greater (by 2 mm Hg) readings.

Gustin et al[57] conducted a review of the medical records of 127 hypertensive patients who switched therapy from long-acting nifedipine to felodipine. This switch resulted in slightly lower diastolic blood pressure measurements (78 vs 80 mm Hg; $P<0.05$). Side effects reported and supplemental medication use were similar between the agents.

Impact on Physician Visits
In a study by Sheehy et al[52], a comparative review of patients receiving amlodipine or felodipine found an increased number of specialist visits in the amlodipine group (odds ratio, 1.14; 95% CI, 1.08 to 1.20); however, this same group of patients receiving amlodipine had significantly better compliance and refill rates and fewer medication switches.

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity Dihydropyridines

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
amlodipine	tablet	Norvasc®*	$$$	$$
felodipine	sustained-release tablet	Plendil®*	$$$	$$$
isradipine	capsule, sustained-release tablet	DynaCirc®†*, DynaCirc CR®	$$$$	$$$
nicardipine	capsule, injection, sustained-release capsule	Cardene®*, Cardene SR®	$$$	$
nifedipine	capsule, sustained-release tablet	Adalat CC®*, Procardia®*, Procardia XL®*	$$$	$$$

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
nimodipine	capsule	Nimotop®*	$$$$$	$$$$$
nisoldipine	sustained-release tablet	Sular®	$$$	N/A

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

Dihydropyridine calcium-channel blocking agents are effective in the treatment of hypertension, as demonstrated in clinical trials and confirmed in recommendations by national organizations. A few of the dihydropyridine agents, amlodipine, nicardipine, and nifedipine, can be used to manage angina as well. For some patients, such as those with hypertension and chronic stable angina, a calcium-channel blocking agent may be a first choice; however for most patients, they are second-line or adjunct treatment options.[12]

Within-class differences are seen among the dihydropyridines. Available comparisons of amlodipine and felodipine for the treatment of hypertension favor amlodipine for compliance and the achievement of blood pressure goals.[47,48] Other within-class comparisons showed minor statistical differences between agents in lowering blood pressure; however the clinical significance of these small differences was not evaluated in the trials.[49-56] There is no agent that is clearly more efficacious than the others within the class.[49-56] In terms of between-class comparisons, Ribeiro et al found amlodipine to be more effective than losartan at lowering blood pressure; however, in a comparison of amlodipine to a different angiotensin II receptor blocker, this result was not repeated.[60]

The role of dihydropyridine agents in cardiovascular outcomes has been studied and some of these studies demonstrated no benefit over placebo, while others showed benefits greater than placebo and/or similar to those of β-blockers, diuretics and angiotensin-converting enzyme inhibitors.[64-76] National, international and professional guidelines can be used to direct the use of the dihydropyridines for their various indications and compelling uses.

Currently, all but two of the dihydropyridine calcium-channel blocking agents are available as generic products, and neither of these offers a significant clinical advantage in terms of efficacy or safety over all other dihydropyridines. Short-acting agents, such as immediate release nifedipine, may increase mortality in post-myocardial infarction (MI) patients and may increase the risk of MI in patients with hypertension. Therefore, short-acting calcium-channel blockers are not recommended in patients with cardiovascular disease.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity dihydropyridine calcium-channel blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Dihydropyridines
Combination Products
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I. Overview

Calcium-channel blocking agents (also called calcium-channel blockers or CCBs) have multiple roles in treating cardiovascular disease. The movement of calcium ions (Ca^{2+}) is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac muscle and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.[1-3] Calcium-channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked, which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance.[4,5] In addition, calcium-channel blocking agents decrease peripheral vascular resistance by relaxing arteriolar smooth muscle.[6] Both coronary and systemic vasodilation serve to reduce cardiac workload.[7] There are two classes of CCBs: dihydropyridines, which are similar in chemical structure, and nondihydropyridines, which are a structurally miscellaneous group. The nondihydropyridines have additional effects and thus a somewhat different therapeutic profile from the dihydropyridines.[1,4,8,9] These classes are covered in separate reviews.

Dihydropyridines are potent vasodilators due to greater selectivity for vascular smooth muscle.[2] They have little, or even no effect, upon cardiac muscle contractility or conduction. Amlodipine, a dihydropyridine calcium-channel blocking agent, is combined with olmesartan or valsartan in the products in this review. Olmesartan and valsartan are angiotensin II receptor antagonists (also known as angiotensin II receptor blockers, or ARBs). These agents interfere with the renin-angiotensin-aldosterone system, which plays an influential role in blood pressure control. The binding of angiotensin II to its receptors results in vasoconstriction, as well aldosterone secretion. When these agents block the binding of angiotensin II, the resultant vasoconstriction and aldosterone release does not occur, therefore reducing blood pressure.[10,11] By combining agents with different mechanisms of action, the resultant vasodilation can be more potent or effective than either agent used alone. The combination products reviewed here, amlodipine plus olmesartan and amlodipine plus valsartan, are indicated for the treatment of hypertension in adults.[12,13]

The combination dihydropyridines that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. No products in this class are available generically. At present, the dihydropyridine component, amlodipine, is available generically, but olmesartan and valsartan are only available as branded products.

Table 1. Combination Dihydropyridines Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
amlodipine and olmesartan	tablet	Azor®	none
amlodipine and valsartan	tablet	Exforge®	none

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the combination dihydropyridines are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of acute myocardial infarction, angina pectoris, chronic heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Combination Dihydropyridines

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[14]	• Angiotensin receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an angiotensin converting enzyme (ACE) inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a left ventricular ejection fraction of ≤40%. • ARBs may be considered in combination with an ACE inhibitor due to left ventricular systolic dysfunction. • Long-acting calcium-channel blocking agents (CCBs) or long-acting nitrates may be used if β-adrenergic blocking agents (β-blockers) are contraindicated. Immediate-release and short-acting dihydropyridine CCBs can increase adverse cardiac events and should not be used. • Long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful.
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[15]	• Nitrates, morphine, β-blockers, CCBs, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet agents, and GP IIb/IIIa receptor antagonists can be used in the acute setting during early hospitalization. • ACE inhibitors should be initiated and continued indefinitely in patients with heart failure, left ventricular dysfunction, diabetes, or hypertension unless contraindicated. ARBs should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and signs of heart failure and left ventricular ejection fraction <40%. • Patients who cannot tolerate ACE inhibitors may be treated with an ARB if they have signs of heart failure and left ventricular ejection fraction <40%. • CCBs are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. • Treatment with nitrates and CCBs is recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions. • Nitrates, β-blockers, and CCBs (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)**[16]	<u>Therapy to Improve Prognosis</u> • CCBs may be recommended in patients with angina who cannot tolerate β-blockers and who have had an MI and who do not have heart failure. <u>Symptomatic Treatment and Treatment of Ischemia</u> • If patients are intolerant to β-blocker therapy, consideration may be given to a CCB or a long-acting nitrate. Sinus node inhibition may be considered. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. If combination β-blocker and CCB therapy is insufficient, a long-acting nitrate may be substituted for the CCB. <u>Treatment of Syndrome X</u> • Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination. <u>Treatment of Vasospastic/Variant Angina</u> • Treatment with CCBs is recommended. Nitrates may also be used if needed.

Clinical Guideline	Recommendation
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS) (2007)**[17]	• CCBs may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina. • Nondihydropyridine CCBs should not be used unless combined with β-blockers. • ARBs should be considered in patients intolerant to ACE inhibitors and/or who have heart failure or have had an MI with a left ventricular ejection fraction of ≤40%.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease (2004)**[18]	Symptomatic Patients • The following agents are recommended to reduce symptoms only: nitroglycerine (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when monotherapy has been unsuccessful.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[19]	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors, and β-blockers have been shown to prevent heart failure. The ARBs losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. • Blood sugar in patients with diabetes should be controlled according to contemporary guidelines. ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, MI, and heart failure. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left ventricular dysfunction or hypertension. • ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes, and hypertension with other cardiovascular risk factors. Patients With Cardiac Structural Abnormalities or Remodeling Who Have not Developed Heart Failure Symptoms (Stage B) • ARBs are recommended for patients with reduced left ventricular ejection fraction and a history of an MI if they are intolerant to ACE inhibitors. • ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy. • CCBs with negative inotropic effects are not recommended in asymptomatic patients with low ejection fraction after an MI. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • ARBs approved for the treatment of heart failure are recommended in all patients intolerant to ACE inhibitors with current or past symptoms of heart failure and reduced left ventricular ejection fraction. • Drugs known to adversely affect patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction (nonsteroidal anti-inflammatory drugs (NSAIDs), some CCBs, some antiarrhythmic medications) should be discontinued and avoided if possible. • ARBs are reasonable alternatives to ACE inhibitors as first-line therapy in patients with mild-to-moderate heart failure and reduced left ventricular ejection fraction. • The combination of a nitrate and hydralazine is reasonable in patients who are intolerant to ACE inhibitor and ARB therapy or in whom therapy with one of these agents is contraindicated.

Clinical Guideline	Recommendation
	• The addition of an ARB is reasonable in patients who are symptomatic despite conventional treatment. • The routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended. • CCBs are not recommended as routine treatment for heart failure. <u>Patients With Heart Failure and Normal Left Ventricular Ejection Fraction</u> • β-Blockers, ARBs, ACE inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[20]	<u>Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction</u> • ACE inhibitors are recommended. ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of ACE inhibitors and ARBs together is not recommended. <u>Patients With Left Ventricular Systolic Dysfunction</u> • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had an MI and in patients with chronic heart failure and systolic dysfunction. <u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease (CVD) or diabetes and at least 1 other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • CCBs should be considered in patients who have hypertension (amlodipine should be considered) or angina, and in those who have atrial fibrillation requiring ventricular rate control and are intolerant to β-blockers. <u>Patients With Heart Failure and Coronary Artery Disease</u> • CCBs should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Managing Patients With Heart Failure and Hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or CCB. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent. • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing CCB (amlodipine) may be considered. <u>Managing Heart Failure in the Elderly, Women, and African Americans</u> • ACE inhibitor and β-blocker therapy are recommended in all African American

Clinical Guideline	Recommendation
	patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)**[21]	• ARBs may be used in patients who are intolerant to ACE inhibitor therapy. They may also be used in combination with ACE inhibitors in patients who remain symptomatic. • The CCBs diltiazem and verapamil are not recommended in patients with heart failure caused by systolic dysfunction. The addition of felodipine or amlodipine does not improve survival or symptoms, though may be helpful in patients with angina or arterial hypertension not controlled with nitrates and β-blockers.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[22]	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting CCBs may also be used. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients. • CCBs may be useful in Raynaud's syndrome and certain arrhythmias. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.

Clinical Guideline	Recommendation
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[23]	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[24]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated. • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[25]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[26]	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • Initial therapy in patients younger than 55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[27]	• No specific recommendation is made concerning combination dihydropyridines.

Clinical Guideline	Recommendation
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[28]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2. • Multiple drug therapy is generally required to achieve blood pressure goals.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[29]	• All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[30]	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)**[31]	<u>Secondary Prevention</u> • ARBs are recommended in patients who are intolerant to ACE inhibitors and have heart failure or who have a left ventricular ejection fraction of ≤40%. • ARBs should be considered in all patients intolerant to ACE inhibitor therapy.
National Institute for Health and Clinical Excellence (NICE): **Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a**	• ARBs are recommended in patients who are intolerant to ACE inhibitor therapy. • In patients with a proven MI in the past and with asymptomatic left ventricular systolic dysfunction and in those without heart failure and preserved left ventricular function, ACE inhibitors are recommended (ARBs may be given to patients who are intolerant of ACE inhibitors). • CCBs should not routinely be used to reduce cardiovascular risk after an MI. • Verapamil or diltiazem may be considered for secondary prevention in patients

Clinical Guideline	Recommendation
Myocardial Infarction (2007)[32]	without pulmonary congestion or left ventricular systolic dysfunction in whom β-blockers must be discontinued or in whom β-blockers are contraindicated.
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)**[33]	Prophylactic Therapies in the Acute Phase • There is no case for using CCBs for prophylactic purposes in the acute phase of an MI. Secondary Prevention • Diltiazem or verapamil may be appropriate if β-blockers are contraindicated in the absence of heart failure. • Dihydropyridines have not been shown to improve prognosis and should only be used for clear clinical indications.

III. Indications

Food and Drug Administration (FDA)-approved indications for the combination dihydropyridines 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 Combination Dihydropyridines[12,13]

Indication	Amlodipine and Olmesartan*	Amlodipine and Valsartan*
Hypertension	✔ †	✔

*Not indicated for initial therapy of hypertension.
†Alone or in combination with other antihypertensive drugs.

IV. Pharmacokinetics

The pharmacokinetic parameters of the combination dihydropyridines are noted in Table 4.

Table 4. Pharmacokinetic Parameters of the Combination Dihydropyridines[10-13]

Drug	Bio-availability (%)	Protein Binding (%)	Elimination	Active Metabolites	Serum Half-Life (hours)
Amlodipine	64-90	93	10% of parent compound and 60% of inactive metabolites are excreted in the urine	None	30-50
Olmesartan	26	99	35%-50% is excreted in the urine with the remainder excreted in the feces	Olmesartan*	13
Valsartan	10-35	95	83% excreted in the feces as unchanged drug and 13% in the urine as unchanged drug	None	6

*Azor® contains olmesartan medoxomil, a prodrug, which is metabolized to active olmesartan.

V. Drug Interactions

Significant drug interactions with the combination dihydropyridines are noted in Table 5.

Table 5. Significant Drug-Drug Interactions with the Combination Dihydropyridines[34]

Drug(s)	Significance Level	Interaction	Mechanism
Olmesartan, valsartan	1	Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	Elevated serum potassium concentrations in high-risk patients may occur. Close monitoring of serum potassium and renal function is recommended.

Drug(s)	Significance Level	Interaction	Mechanism
Valsartan	2	Lithium	Elevations in plasma lithium levels may occur. Close monitoring for lithium toxicity and possible dose adjustment is recommended.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

Adverse drug reactions for the combination dihydropyridines are noted in Table 6. All brand combination dihydropyridine preparations bear a boxed warning mandated by the Food and Drug Administration (FDA) regarding the use of these drugs during pregnancy. These boxed warnings appear in Tables 7 and 8.

Table 6. Adverse Drug Events (%) Associated with the Combination Dihydropyridines[11-13,35]

Adverse Event	Amlodipine and Olmesartan	Amlodipine and Valsartan
Cardiovascular		
Arrhythmia	-	✔
Atrial fibrillation	-	1.0
Bradycardia	-	1.0
Cardiac murmur	-	✔
Chest pain	-	1.0
Hypotension	✔	✔
Orthostatic hypotension	✔	1.0
Palpitations	0.7-4.5	✔
Peripheral ischemia	-	1.0
Postural hypotension	-	1.0
Pulse irregularity	-	✔
Tachycardia	-	✔
Vasculitis	-	1.0
Ventricular tachycardia	-	1.0
Central Nervous System		
Abnormal dreams	-	1.0
Agitation	-	✔
Amnesia	-	✔
Anxiety	-	3.0
Apathy	-	✔
Asthenia	✔	✔
Ataxia	-	✔
Carpal tunnel syndrome	-	✔
Cervicobrachial syndrome	-	✔
Depersonalization	-	1.0
Depression	-	✔
Dizziness	1.1-3.4	2.1
Headache	-	11.0
Hypoesthesia	-	✔
Insomnia	-	✔
Migraine	-	✔
Nervousness	-	1.0
Paresthesia	-	✔
Peripheral neuropathy	-	1.0
Postural dizziness	-	1.0
Sciatica	-	✔
Sinus headache	-	✔

Adverse Event	Amlodipine and Olmesartan	Amlodipine and Valsartan
Somnolence	0.3-1.6	3.0
Syncope	-	1.0
Tremor	-	1.0
Vertigo	-	✔
Dermatologic		
Alopecia	✔	✔
Cold and clammy skin	-	✔
Dermatitis	-	✔
Eczema	-	✔
Erythema	-	✔
Erythema multiforme	-	1.0
Exanthema	-	✔
Flushing	0.7-4.5	✔
Hyperhidrosis	-	✔
Pruritus	✔	✔
Rash	✔	✔
Rash, erythematous	-	1.0
Rash, maculopapular	-	1.0
Skin discoloration	-	✔
Skin dryness	-	✔
Urticaria	✔	✔
Endocrine and Metabolic		
Gout	-	✔
Gynecomastia	✔	-
Diabetes mellitus (Type II)	-	✔
Hypercholesterolemia	-	✔
Hyperglycemia	-	1.0
Thirst	-	1.0
Gastrointestinal		
Abdominal discomfort	-	✔
Abdominal distension	-	✔
Abdominal pain	-	3.0
Anorexia	-	1.0
Colitis	-	✔
Constipation	-	✔
Diarrhea	-	3.0
Dry mouth	-	✔
Dyspepsia	-	✔
Dysphagia	-	1.0
Flatulence	-	✔
Gastritis	-	✔
Gastroenteritis	-	✔
Hemorrhoids	-	✔
Increased appetite	-	✔
Jaundice	✔	-
Loose stools	-	✔
Nausea	-	3.0
Pancreatitis	-	1.0
Vomiting	✔	✔
Genitourinary		
Cystitis	-	✔
Dysuria	-	✔

Adverse Event	Amlodipine and Olmesartan	Amlodipine and Valsartan
Erectile dysfunction	-	✔
Hematuria	-	✔
Impotence	-	✔
Micturition disorder	-	1.0
Nephrolithiasis	-	✔
Nocturia	✔	1.0
Pollakiuria	-	✔
Polyuria	-	✔
Sexual dysfunction	-	1.0
Urinary frequency	✔	✔
Urinary tract infection	-	✔
Hematological		
Leukopenia	-	1.0
Purpura	-	1.0
Thrombocytopenia	-	1.0
Laboratory Abnormalities		
Blood urea nitrogen increases	-	5.5-16.6
Creatinine increases	-	✔
Hepatic enzyme elevations	✔	✔
Hyperkalemia	-	3.0-10.0
Musculoskeletal		
Arthralgia	-	✔
Arthrosis	-	1.0
Back pain	-	✔
Hypertonia	-	✔
Joint sprain	-	✔
Joint swelling	-	✔
Limb injury	-	✔
Muscle cramps	-	1.0
Muscle spasms	-	✔
Muscle weakness	-	✔
Musculoskeletal chest pain	-	✔
Myalgia	-	✔
Osteoarthritis	-	✔
Rhabdomyolysis	✔	-
Twitching	-	✔
Respiratory		
Bronchitis	-	✔
Cough	-	2.0
Dysphonia	-	✔
Dyspnea	-	1.0
Epistaxis	-	✔
Influenza	-	2.0
Nasal congestion	-	✔
Seasonal allergies	-	✔
Sinus congestion	-	✔
Sinusitis	-	✔
Upper respiratory tract infection	-	2.9
Other		
Abnormal visual accommodation	-	✔
Acute renal failure	✔	✔
Allergic reaction	✔	1.0

Adverse Event	Amlodipine and Olmesartan	Amlodipine and Valsartan
Angioedema	✔	1.0
Conjunctivitis	-	1.0
Contusion	-	✔
Diplopia	-	1.0
Eye pain	-	1.0
Ear pain	-	✔
Edema	1.8-14.6	✔
Epicondylitis	-	✔
Fatigue	-	✔
Gingival hyperplasia	-	1.0
Hot flush	-	✔
Hypersensitivity	-	✔
Lymphadenopathy	-	✔
Malaise	-	1.0
Nasopharyngitis	-	4.3
Pain	-	✔
Parosmia	-	✔
Peripheral edema	18.0-26.0	5.0-8.0
Pharyngitis	-	✔
Pharyngolaryngeal pain	-	✔
Pharyngotonsillitis	-	✔
Pitting edema	-	✔
Pneumonia	-	✔
Post-procedural pain	-	✔
Pyrexia	-	✔
Rhinitis	-	✔
Rigors	-	1.0
Taste perversion	-	✔
Tinnitus	-	✔
Tooth abscess	-	✔
Toothache	-	✔
Tonsillitis	-	✔
Viral infection	-	✔
Visual disturbance	-	✔
Weight gain	-	1.0
Weight loss	-	1.0
Xerophthalmia	-	✔

✔ Percent not specified.
-Event not reported or incidence <1%.

Table 7. Black Box Warning for Amlodipine and Olmesartan[12]

WARNING
USE IN PREGNANCY When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, amlodipine-olmesartan should be discontinued as soon as possible. (See also WARNINGS and PRECAUTIONS.)

Table 8. Black Box Warning for Amlodipine and Valsartan[13]

WARNING
USE IN PREGNANCY When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, amlodipine-valsartan should be discontinued as soon as possible. (See also WARNINGS: Fetal/Neonatal Morbidity and Mortality.)

VII. Dosing and Administration

The usual dosing regimens for the combination dihydropyridines are summarized in Table 9.

Table 9. Usual Dosing for the Combination Dihydropyridines[11-13,35]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amlodipine and olmesartan*	Initial: amlodipine 5 to 10 mg and olmesartan 20 to 40 mg once daily Maximum: amlodipine 10 mg and olmesartan 40 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg-20 mg 5 mg-40 mg 10 mg-20 mg 10 mg-40 mg
Amlodipine and valsartan†	Initial: amlodipine 5 to 10 mg and valsartan 160 to 320 mg once daily Maximum: amlodipine 10 mg and valsartan 320 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg-160 mg 5 mg-320 mg 10 mg-160 mg 10 mg-320 mg

*Dose may be substituted for the individually titrated components.
†Therapy should begin only after a patient has failed to achieve blood pressure control with monotherapy with one or both of the active components.

VIII. Effectiveness

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

Table 10. Comparative Clinical Trials Using the Combination Dihydropyridines

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Philipp et al[36] (Study 1) Amlodipine 2.5 to 5 mg QD vs valsartan 40 to 320 mg QD vs amlodipine 2.5 to 5 mg with valsartan 40 to 320 mg QD vs placebo	DB, MC (multinational), PC, PG, RCT Males and females, ages 18 years and older with hypertension (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=1,911 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 2)	Primary: All treatments significantly decreased mean sitting DBP from baseline (*P*<0.05). Combination treatment resulted in significantly greater blood pressure reduction than either monotherapy (*P*<0.05 for all combinations compared to respective doses of monotherapy except amlodipine 2.5 mg and valsartan 40 mg QD). Secondary: All treatments significantly decreased mean sitting SBP from baseline (*P*<0.05). Combination treatment resulted in significantly greater blood pressure reduction than either monotherapy (*P*<0.05 for all combinations compared to respective doses of monotherapy). Response rates were significantly different from placebo for all treatment groups (*P*<0.05). Response rates for combination products were significantly different than each monotherapy for the following combinations: amlodipine 5 mg plus valsartan 80 mg, amlodipine 5 mg plus valsartan 40 mg and amlodipine 2.5 mg plus valsartan 80 mg (*P*<0.05 for each combination compared to both monotherapy). Response rates for all combinations produced significantly improved compared to either one of the monotherapies except amlodipine 2.5 mg plus valsartan 40 mg (*P*<0.05 for each combination compared to one of the respective monotherapy). Control rates with therapy were significantly better than placebo, with the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				highest control rate achieved with amlodipine 5 mg plus valsartan 320 mg (*P*<0.05 compared to placebo, *P* value not reported for others). Adverse event rates were not significantly different among combination treatment, amlodipine treatment, and placebo. Adverse event rates were significantly different between amlodipine plus valsartan and valsartan monotherapy (*P*<0.05). The most commonly reported adverse events for combination treatment were: peripheral edema, headache, nasopharyngitis, upper respiratory tract infection and dizziness. Peripheral edema occurred significantly less frequently in the combination treatment group than the amlodipine monotherapy group (5.4% vs 8.7%; *P*=0.014) and significantly more frequently than in the valsartan monotherapy group (5.4% vs 2.1%; *P*<0.001). Peripheral edema occurrence in the valsartan group was similar to the rate in the placebo group.
Philipp et al[36] (Study 2) Amlodipine 10 mg QD vs valsartan 160 to 320 mg QD vs amlodipine 10 mg with valsartan 160 or 320 mg QD vs placebo	DB, MC (multinational), PC, PG, RCT Male and females, ages 18 years and older with hypertension (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=1,250 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 1)	Primary: Mean sitting DBP was significantly reduced for both combination as compared to the individual components and to placebo (*P*<0.05). Secondary: Response rates and control rates for combination treatments were significantly greater than valsartan monotherapy therapy and placebo therapy, but not different from amlodipine monotherapy (*P*<0.05). Adverse event rates were not significantly different between combination treatment, amlodipine treatment and placebo. Adverse event rates were significantly different between amlodipine plus valsartan and valsartan monotherapy (*P*<0.05).
Poldermans et al[37]	AC, DB, MC, PG, RCT	N=130	Primary: Safety/adverse events,	Primary: Both treatments were well tolerated, 26 (40.6%) of patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Amlodipine 5 to 10 mg QD plus valsartan 160 mg QD vs lisinopril 10 to 20 mg plus HCTZ 12.5 mg QD	Males and females, ages 18 years and older with hypertension (mean DBP ≥110 mm Hg and <120 mm Hg)	6 weeks	vital signs, hematology, biochemistry variables Secondary: Efficacy (mean DBP, response rate, proportion of patients with mean DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline)	amlodipine and valsartan and 21 (31.8%) of patients receiving lisinopril and HCTZ reported an adverse events and most were not considered drug related (*P* value not reported). Peripheral edema was reported more often in the amlodipine and valsartan group than the lisinopril and HCTZ group (7.7% vs 1.5%) and cough was reported less often in the amlodipine and valsartan group than the receiving lisinopril and hydrochlorothiazide group (1.6% vs 3.0%). No difference was found between the treatments in changes in laboratory values or biochemistry variables. Secondary: Both treatments resulted in significant reductions from baseline in mean SBP and DBP (*P*<0.0001 for both from baseline) but were not significantly different from each other. Mean blood pressure for each group at study end: amlodipine and valsartan 135.0/83.6 mm Hg and lisinopril and HCTZ 138.7/85.2 mm Hg. The response rate was similar between the groups, 100% vs 95.5% (*P* value not significant).
Chrysant et al[38] COACH Amlodipine 5 or 10 mg QD vs olmesartan 10, 20 or 40 mg QD vs Each possible combination of above	DB, factorial, MC, PC, RCT Patients, age 18 years and older, with seated DBP of 95 to 120 mm Hg	N=1,940 8 weeks	Primary: Change from baseline in seated DBP at week 8 Secondary: Change from baseline in seated SBP at week 8 Mean change from baseline in seated DBP and SBP at weeks 2, 4, 6 and 8 without last observation carried forward Proportion of patients	Primary: All active treatments and placebo resulted in significant decreases in seated DBP at week 8 (*P*<0.001). Reductions in seated DBP with monotherapy treatment ranged from –8.3 to –12.7 mm Hg; reductions with combination therapy ranged from –13.8 to –19.0 mm Hg. All combinations reduced seated DBP significantly greater than either component as monotherapy at the same dosage (*P*<0.001). Secondary: All active treatments and placebo resulted in significant decreases in seated SBP at week 8 (*P*<0.001 for treatment, *P*=0.024 for placebo). All combinations reduced seated SBP significantly greater either component as monotherapy at the same dosage (*P*<0.001). The proportion of patients achieving goal BP were: 20.0% to 36.3% of patients receiving olmesartan monotherapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amlodipine doses with above olmesartan doses: 5/10, 5/20, 5/40, 10/10, 10/20, 10/40 vs placebo			achieving BP goal (<140/90 mm Hg or <130/80 mm Hg) Safety: adverse events and laboratory monitoring	21.1% to 32.5% of patients receiving amlodipine monotherapy 35.0% to 53.2% of patients receiving combination therapy 8.8% of patients receiving placebo Combination therapy resulted in significantly greater achievement of goal BP than monotherapy (*P*<0.005). No difference in overall rates of adverse events across the different treatment groups was seen. 26.9% of patients experienced a drug-related adverse event. Changes in laboratory values were not considered clinically significant nor followed a consistent pattern with treatment: none of the changes were considered clinically significant. Platelet counts increased significantly from baseline (statistically) for patients receiving amlodipine, however the increase was <10% and not deemed clinically relevant.

Drug regimen abbreviations: QD=once daily
Study abbreviations: AC=active-controlled, DB=double-blind, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

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

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

Rx=prescription.

Table 11. Relative Cost of the Combination Dihydropyridines

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
amlodipine and olmesartan	tablet	Azor®	$$$	N/A
amlodipine and valsartan	tablet	Exforge®	$$$	N/A

No generic products are available in this class.
N/A=not available.

X. Conclusions

Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) states that a majority of patients will require combination therapy to achieve goal blood pressure.[22]

The combination of amlodipine and valsartan has demonstrated efficacy in reducing blood pressure.[36,37] Clinical trials have shown that the combination of these two drugs are more effective than each agent given as monotherapy. The amlodipine/valsartan combination has also been shown to be as effective as the combination of lisinopril and hydrochlorothiazide, while demonstrating a similar safety profile.[37] In a recently published clinical trial, amlodipine and olmesartan used in combination demonstrated better efficacy in reducing blood pressure in approximately 1,900 patients with hypertension compared to those who used the two active ingredients as separate products. [38] Reported adverse events were similar between monotherapies and combination treatment.[12,36-38] Combination products offer an effective option for treating patients who require two medications to control blood

pressure. The selection of anti-hypertensive agents to be used in combination should be made based upon a patient's other co-morbidities, as additional benefits may be derived from specific individual drugs.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand combination dihydropyridine calcium-channel blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Miscellaneous Calcium-Channel Blocking Agents
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I. Overview

Calcium-channel blocking agents have multiple roles in treating cardiovascular disease. The movement of calcium ions (Ca^{2+}) is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac muscle and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.[1-3] Calcium-channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked, which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance.[4,5] In addition, calcium-channel blocking agents (also called calcium-channel blockers or CCBs) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle.[6] Both coronary and systemic vasodilation serve to reduce cardiac workload.[7] There are two classes of CCBs: dihydropyridines, which are similar in chemical structure, and nondihydropyridines, which are a structurally miscellaneous group.

This review covers the nondihydropyridine, or miscellaneous, calcium-channel blocking agents. They have additional effects and thus a somewhat different therapeutic profile from the dihydropyridines.[1,4,8,9] Generally, the miscellaneous agents produce less peripheral vasodilation than the dihydropyridines, with verapamil producing less than diltiazem. Additionally, diltiazem and verapamil slow conduction in the atrioventricular (AV) node, slowing the heart rate.[2,10,11]

The primary effect of verapamil, a diphenylalkylamine calcium-channel blocking agent, is to slow conduction through the AV node. Verapamil has negative inotropic and chronotropic effects. Because of these properties, it reduces heart rate and systemic blood pressure.[10] Verapamil is Food and Drug Administration (FDA) indicated for the treatment of arrhythmias, chronic stable angina, hypertension, unstable and vasospastic angina.[12-18]

Diltiazem's effect on cardiac tissue is slightly different than the effect of verapamil. Diltiazem is a benzothiazepine and a potent vasodilator of coronary arteries. Although diltiazem does decrease AV node conduction, it does not have negative inotropic properties. Like verapamil, it reduces heart rate and systemic blood pressure.[11] Diltiazem is FDA indicated for the treatment of chronic stable and variant angina, arrhythmias, and hypertension.[19-25]

Both diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action. There are numerous generic formulations for diltiazem and verapamil. The intravenous (IV) formulations of the miscellaneous calcium-channel blocking agents are administered primarily on an inpatient basis in institutions. Since they are not routinely dispensed in an outpatient pharmacy, these formulations, and their use in the treatment of cardiac arrhythmias, will not be discussed in this review.

The miscellaneous calcium-channel blocking agents included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Miscellaneous Calcium-Channel Blocking Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
diltiazem	controlled-release capsule, injection, sustained-release capsule, sustained-release tablet, tablet	Cardizem®*, Cardizem CD®*, Cardizem LA®, Dilacor XR®*, Tiazac®*	diltiazem

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
verapamil	extended-release capsule, injection, sustained-release tablet, tablet	Calan®*, Calan SR®*, Covera-HS®, Isoptin SR®*, Verelan®*, Verelan PM®*	verapamil

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the miscellaneous calcium-channel blocking agents are summarized in Table 2. For a comprehensive overview of the pharmacologic management of acute myocardial infarction, angina pectoris, chronic heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Miscellaneous Calcium-Channel Blocking Agents

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[26]	• Long-acting calcium-channel blocking agents (CCBs) or long-acting nitrates may be used if β-adrenergic blocking agents, (β-blockers) are contraindicated. Immediate-release and short-acting dihydropyridine CCBs can increase adverse cardiac events and should not be used. • Long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful.
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[27]	• Nitrates, morphine, β-blockers, CCBs, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet agents, and GP IIb/IIIa receptor antagonists can be used in the acute setting during early hospitalization. • CCBs are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. • Treatment with nitrates and CCBs is recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions. • Nitrates, β-blockers, and CCBs (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)**[28]	<u>Therapy to Improve Prognosis</u> • CCBs may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction (MI) and who do not have heart failure. <u>Symptomatic Treatment and Treatment of Ischemia</u> • If patients are intolerant to β-blocker therapy, consideration may be given to a CCB or a long-acting nitrate. Sinus node inhibition may be considered. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. If combination β-blocker and CCB therapy is insufficient, a long-acting nitrate may be substituted for the CCB. <u>Treatment of Syndrome X</u> • Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination. <u>Treatment of Vasospastic/Variant Angina</u> • Treatment with CCBs is recommended. Nitrates may also be used if needed.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-**	• CCBs may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina. • Nondihydropyridine CCBs should not be used unless combined with β-blockers.

Clinical Guideline	Recommendation
Segment Elevation Acute Coronary Syndromes (NSTE ACS) (2007)[29]	
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease (2004)[30]**	Symptomatic Patients • The following agents are recommended to reduce symptoms only: nitroglycerine (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when monotherapy has been unsuccessful.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)[31]**	Patients With Cardiac Structural Abnormalities or Remodeling Who Have not Developed Heart Failure Symptoms (Stage B) • CCBs with negative inotropic effects are not recommended in asymptomatic patients with low ejection fraction after an MI. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Drugs known to adversely affect patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction (nonsteroidal anti-inflammatory drugs (NSAIDs), some CCBs, some antiarrhythmic medications) should be discontinued and avoided if possible. • CCBs are not recommended as routine treatment for heart failure. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • β-Blockers, angiotensin receptor blocker (ARBs), angiotensin converting enzyme (ACE) inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)[32]**	Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • CCBs should be considered in patients who have hypertension (amlodipine should be considered) or angina, and in those who have atrial fibrillation requiring ventricular rate control and are intolerant to β-blockers. Patients With Heart Failure and Coronary Artery Disease • CCBs should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. Managing Patients With Heart Failure and Hypertension • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or CCB. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent. • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing CCB (amlodipine) may be considered.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis**	• The CCBs diltiazem and verapamil are not recommended in patients with heart failure caused by systolic dysfunction. The addition of felodipine or amlodipine does not improve survival or symptoms, though may be helpful in patients with

Clinical Guideline	Recommendation
and Treatment of Chronic Heart Failure: Executive Summary (2005)[33]	angina or arterial hypertension not controlled with nitrates and β-blockers.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[34]	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting CCBs may also be used. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease (CVD) and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2 to 4 times higher in African American patients. • CCBs may be useful in Raynaud's syndrome and certain arrhythmias.ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[35]	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[36]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
Treatment Guidelines from the	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor

Clinical Guideline	Recommendation
Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[37]	or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[38]	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[39]	• No specific recommendation is made concerning miscellaneous calcium-channel blocking agents.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[40]	• No specific recommendation is made concerning miscellaneous calcium-channel blocking agents.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[41]	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[42]	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction**	• No specific recommendation is made concerning miscellaneous calcium-channel blocking agents.

Clinical Guideline	Recommendation
(STEMI) (2007)[43]	
National Institute for Health and Clinical Excellence (NICE): **Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)[44]**	• CCBs should not routinely be used to reduce cardiovascular risk after an MI. • Verapamil or diltiazem may be considered for secondary prevention in patients without pulmonary congestion or left ventricular systolic dysfunction in whom β-blockers must be discontinued or in whom β-blockers are contraindicated.
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)[45]**	Prophylactic Therapies in the Acute Phase • There is no case for using CCBs for prophylactic purposes in the acute phase of an MI. Secondary Prevention • Diltiazem or verapamil may be appropriate if β-blockers are contraindicated in the absence of heart failure. • Dihydropyridines have not been shown to improve prognosis and should only be used for clear clinical indications.

III. Indications

Food and Drug Administration (FDA)-approved indications for the miscellaneous calcium-channel blocking 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 Miscellaneous Calcium-Channel Blocking Agents[12-25]

Drug	Example Brand Name(s)	Hyper-tension	Chronic Stable Angina	Unstable Angina	Vasospastic Angina (Prinzmetal's or Variant Angina)	Atrial Fibrillation/ Atrial Flutter	Paroxysmal Supraventricular Tachycardia (PSVT)
Diltiazem IR tablets	Cardizem®*		✔		✔ ‡		
Diltiazem, SR tablets	Cardizem LA®	✔ §	✔				
Diltiazem ER capsules (twice-daily formulation)	Cardizem SR®†	✔ §					
Diltiazem ER capsules (once-daily formulations)	Cardizem CD®*, Dilacor XR®*, Tiazac®*	✔ §	✔				
Diltiazem IV	N/A					✔ ‖	✔ ¶
Verapamil IR tablets	Calan®*	✔	✔	✔ #	✔	✔ **	✔ ††
Verapamil ER tablets	Calan SR®*, Isoptin SR®*	✔					
Verapamil osmotic-release ER tablets	Covera-HS®	✔	✔				
Verapamil ER capsules	Verelan®*, Verelan PM®*	✔					
Verapamil IV	N/A					✔ ‡‡	✔ §§

ER=extended-release, IR=immediate-release, IV=intravenous, SR=sustained-release
*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
‡Angina due to coronary artery spasm.
§Alone or in combination with other antihypertensive agents.
‖Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
¶Rapid conversion of PSVT to sinus rhythm. This includes atrioventricular (AV) nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome.
#Crescendo, pre-infarction angina.
**In association with digitalis for the control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation.
††Prophylaxis of repetitive paroxysmal supraventricular tachycardia.
‡‡Temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation except when the atrial flutter and/or atrial fibrillation are associated with accessory bypass (WPW and LGL syndromes).
§§Rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory bypass tracts (WPW and LGL syndromes).

IV. Pharmacokinetics

The pharmacokinetic parameters for the miscellaneous calcium-channel blocking agents are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Calcium-Channel Blocking Agents[10-25]

Drug	Bio-availability (%)	Protein Binding (%)	Active Metabolites	Elimination	Half-Life (hours)
Diltiazem IR	40	70-80	Yes	Urine (2%-4% unchanged)	3.0-4.5
Diltiazem ER (twice-daily formulation)	40	70-80	Yes	Urine (2%-4% unchanged)	5-7
Diltiazem ER (once-daily formulations)	41	70-80	Yes	Urine (2%-4% unchanged)	5-10 6-9 (Cardizem LA®) 4-9.5 (Tiazac®)
Verapamil IR	20-35	90	Yes	Urine (70% as metabolites, 3%-4% unchanged), feces (16% or greater)	4.5-12.0
Verapamil ER	20-35	90	Yes	Urine (70% as metabolites, 3%-4% unchanged), feces (16% or greater)	4.5-12.0

ER=extended release; IR=immediate release

V. Drug Interactions

Significant drug interactions with the miscellaneous calcium-channel blocking agents are noted in Table 5.

Table 5. Significant Drug-Drug Interactions with the Miscellaneous Calcium-Channel Blocking Agents[46]

Drug	Significance Level	Interaction	Mechanism
Diltiazem	1	Macrolides (clarithromycin, erythromycin, telithromycin)	Increased serum levels of macrolide antibiotics may result if administered with diltiazem, due to Diltiazem's inhibitory effect on CYP 3A4. Coadministration should be avoided.
Diltiazem	1	Ranolazine	Increased serum levels of ranolazine may result if administered with diltiazem, due to Diltiazem's inhibitory effect on CYP 3A4. Coadministration should be avoided due to the increased risk of QTc prolongation, torsades-de-pointes arrhythmias and death.
Verapamil	1	β-Blockers (acebutolol, atenolol, betaxolol, carteolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propanolol, timolol)	Effects of β-blockers and diltiazem may be increased, close monitoring of cardiac function is recommended. Diltiazem may inhibit the metabolism of some β-blockers (atenolol, metoprolol and propranolol), leading to increased effects of these β-blockers. Monitoring is recommended if these drugs are coadministered.
Verapamil	1	Digoxin	Increased serum levels of digoxin may result, increasing the risk of digoxin toxicity, if administered with verapamil. Both verapamil and digoxin slow cardiac conduction. Close monitoring of digoxin levels is recommended.
Verapamil	1	Dofetilide	Increase serum levels and effects of dofetilide may occur if coadministered with verapamil, increasing the risk of arrhythmia. Coadministration is contraindicated.

Drug	Significance Level	Interaction	Mechanism
Verapamil	1	Macrolides (clarithromycin, erythromycin, telithromycin)	Increased verapamil serum levels and effects may occur if coadministered, due to inhibition of verapamil metabolism by macrolide antibiotics. Close monitoring of cardiac function is recommended if coadministered.
Verapamil	1	Quinidine	Increased effects of quinidine may occur if coadministered with verapamil, increasing the risk of bradycardia, hypotension and ventricular tachycardia, as well as AV block. Coadministration should be avoided.
Verapamil	1	Ranolazine	Increased serum levels of ranolazine may result if administered with verapamil, due to verapamil's inhibitory effect on CYP 3A4 metabolism. Coadministration is contraindicated due to the increased risk of QTc prolongation, torsades-de-pointes arrhythmias and death.
Diltiazem	2	Benzodiazepines (diazepam, midazolam, triazolam)	Increased serum levels of benzodiazepines may result if administered with diltiazem, increasing the risk of CNS depression, due to decreased metabolism of benzodiazepines. If coadministered, the benzodiazepine dose should be decreased.
Diltiazem	2	β-Blockers (atenolol, metoprolol, pindolol, propanolol)	Increased serum levels of β-blockers may result if administered with diltiazem, increasing the risk of symptomatic bradycardia, due to decreased metabolism of β-blockers and additive pharmacologic effects. If bradycardia results, the consider using a lower dose of the β-blocker.
Diltiazem	2	Buspirone	Increased serum levels of buspirone may result if administered with diltiazem, due to Diltiazem's inhibitory effect on CYP 3A4. Close monitoring is recommended.
Diltiazem	2	Carbamazepine	Increased serum levels of carbamazepine may result if administered with diltiazem, increasing the risk of greater effect and toxicity, due to inhibition of carbamazepine metabolism by diltiazem. Close monitoring of carbamazepine levels is recommended and dose alterations may be required if diltiazem is discontinued.
Diltiazem	2	Cyclosporine	Increased serum levels of cyclosporine may result if administered with diltiazem, due to inhibition of cyclosporine metabolism by diltiazem. Close monitoring of cyclosporine levels is recommended.
Diltiazem	2	Digoxin	Increased serum levels of digoxin may result, increasing the risk of digoxin toxicity, if administered with diltiazem, due to decreased renal clearance of digoxin. Close monitoring of digoxin levels is recommended.
Diltiazem	2	Grapefruit	Increased diltiazem serum levels and effects may result if coadministered with grapefruit, due to grapefruit's inhibition of CYP 3A4, reducing the metabolism of diltiazem.
Diltiazem	2	HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Increased serum levels of HMG-CoA reductase inhibitors may result, increasing the risk of toxicities, such as myositis and rhabdomyolysis, if coadministered with diltiazem, due to decreased metabolism of HMG-CoA reductase inhibitors. Close monitoring is recommended if coadministered.
Diltiazem	2	Methylprednisolone	Increased effects of corticosteroids may be seen if administered with diltiazem, due to decreased metabolism of corticosteroids.
Diltiazem	2	Moricizine	Increase levels of moricizine may result, as diltiazem decreases the metabolism of moricizine. Additionally

Drug	Significance Level	Interaction	Mechanism
			moricizine increases the metabolism of diltiazem, resulting in lower serum levels and effects of diltiazem. Close monitoring is recommended.
Diltiazem	2	Quinidine	Increased serum levels of quinidine may result if administered with diltiazem, due to inhibition of quinidine metabolism by diltiazem. Close monitoring of quinidine levels is recommended.
Diltiazem	2	Sirolimus	Increased serum levels of sirolimus may result if administered with diltiazem, due to inhibition of sirolimus metabolism by diltiazem due CYP 3A4 inhibition. Close monitoring of sirolimus levels is recommended.
Diltiazem	2	Tacrolimus	Increased serum levels of tacrolimus may result if administered with diltiazem, due to inhibition of tacrolimus metabolism by diltiazem due CYP 3A4 inhibition. Close monitoring of tacrolimus levels is recommended.
Diltiazem	2	Theophyllines (aminophylline, oxtriphylline, theophylline)	Increased effects of theophyllines may result if administered with diltiazem, due to inhibition of theophylline metabolism by diltiazem. Dose adjustments may be needed.
Verapamil	2	Buspirone	Buspirone's effects may be increased if coadministered with verapamil due to verapamil's inhibitory effect on CYP 3A4 metabolism, reducing the clearance of buspirone.
Verapamil	2	Calcium salts (acetate, carbonate, chloride, citrate, glubionate, gluceptate, gluconate, glycerophosphate, lactate, levulinate)	Effects of verapamil may be decreased by calcium salts. Monitor closely if coadministered.
Verapamil	2	Carbamazepine	Increased serum levels of carbamazepine may result if administered with verapamil, increasing the risk of greater effect and toxicity, due to inhibition of carbamazepine metabolism by verapamil. Close monitoring of carbamazepine levels is recommended and dose alterations may be required if verapamil is discontinued.
Verapamil	2	Cyclosporine	Increased serum levels of cyclosporine may result if administered with verapamil, increasing the risk of nephrotoxicity, due to verapamil's inhibitory effect on cyclosporine metabolism. Close monitoring is recommended and dose adjustments may be required.
Verapamil	2	Ethanol	Ethanol effects may be prolonged, including decreased coordination and judgment if coadministered with verapamil. Verapamil may decrease the metabolism of ethanol. Patients should be warned of this effect.
Verapamil	2	Grapefruit	Increased verapamil serum levels and effects may result if coadministered with grapefruit, due to grapefruit's inhibition of CYP 3A4, reducing the metabolism of verapamil. Coadministration should be avoided.
Verapamil	2	HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Increased serum levels of HMG-CoA reductase inhibitors may result, increasing the risk of toxicities, such as myositis and rhabdomyolysis, if coadministered with verapamil, due to decreased metabolism of HMG-CoA reductase inhibitors. Close monitoring is recommended if coadministered.

Drug	Significance Level	Interaction	Mechanism
Verapamil	2	Nondepolarizing muscle relaxants (atracurium, doxacurium, miva-curium, pancuronium, pipecuronium, tubocurarine)	Increased serum levels of nondepolarizing muscle relaxants may result, increasing the risk of respiratory depression, if coadministered with verapamil, due to calcium's role on muscle contraction. Coadministration should be avoided.
Verapamil	2	Prazosin	Prazosin serum concentrations and effects, decreases in blood pressure, may be increased if coadministered with verapamil. Patients should be monitored and warned about changes in blood pressure.
Verapamil	2	Rifampin	Decreased serum levels of verapamil may result if coadministered with rifampin, due to increased metabolism of verapamil. Dose adjustments or substitutions are recommended if coadministration is required.
Verapamil	2	St. John's Wort	Decreased serum levels of verapamil may result if coadministered with St. John's Wort, due to increased metabolism of verapamil by CYP 3A4. Coadministration should be avoided.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse reactions reported with the miscellaneous calcium channel blocking agents are noted in Table 6.

Table 6. Adverse Drug Events (%) Associated with the Miscellaneous Calcium-Channel Blocking Agents[2, 12-25]

Adverse Event	Diltiazem	Verapamil
Cardiovascular		
Angina	<1	<1
Arrhythmia	<1	-
Asystole	✔	-
Atrial fibrillation	✔	✔
Atrioventricular block	<1-7.6	0.8-1.7
Atrioventricular dissociation	-	<1
Bradycardia	3-6	1.4
Bundle branch block	<1	-
Chest pain	-	<1
Claudication	-	<1
Congestive heart failure	<1	1.9
Electrocardiogram abnormalities/changes	<1-4.1	-
Extrasystoles	<1	-
Hypotension	≤1	0.7-2.5
Myocardial infarction	✔	<1
Palpitations	<1-1.3	<1
Postural hypotension	-	<1
Tachycardia	<1	-
Vasculitis	✔	-
Ventricular tachycardia	-	✔
Central Nervous System		
Abnormal dreams	<1	-
Akathisia	✔	-
Amnesia	<1	-

Adverse Event	Diltiazem	Verapamil
Asthenia	1.2-5	-
Cerebrovascular accident	-	<1
Confusion	-	<1
Depression	<1	-
Dizziness	1.5-7	3.3-4.7
Fatigue	4.8	1.7-4.5
Hallucinations	<1	-
Headache	4.5-12	2.2-6.6
Insomnia	≤1	<1
Nervousness	<1	-
Paresthesia	<1	1.0
Personality changes	<1	-
Psychotic symptoms	-	<1
Somnolence	<1-1.3	<1
Syncope	<1	<1
Tremor	<1	<1
Vertigo	-	<1
Dermatologic		
Alopecia	✔	<1
Dermatitis	✔	-
Ecchymosis	<2	<1
Erythema multiforme (including Stevens-Johnson syndrome)	✔	<1
Exfoliative dermatitis	✔	-
Generalized exanthematous pustulosis	✔	-
Flushing	<1-3	<1
Hair color change	-	✔
Hyperhidrosis	-	<1
Hyperkeratosis	-	<1
Petechiae	<1	-
Photosensitivity	<1	-
Pruritus	<1	-
Rash	1.0-2.0	1.2
Rash, erythema multiforme	✔	-
Rash, maculopapular	-	<1
Urticaria	<1	-
Endocrine and Metabolic		
Gynecomastia	<2	<1
Hyperglycemia	<1	-
Hyperprolactinemia/galactorrhea	-	<1
Hyperuricemia	<1	-
Thirst	<1	-
Gastrointestinal		
Anorexia	<1	-
Constipation	<1-1.6	7.3-11.7
Diarrhea	<1	<1
Dry mouth	<1	<1
Dysgeusia	<1	-
Dyspepsia	<1-1.3	<1
Gingival hyperplasia	✔	<1
Hepatitis	✔	-
Nausea	1.3-1.9	2.1-2.7
Vomiting	<1	-

Adverse Event	Diltiazem	Verapamil
Genitourinary		
Acute renal failure	✔	✔
Albuminuria	<2	-
Crystalluria	<2	-
Impotence	<1	<1
Nocturia	<1	-
Polyuria	<1-1.3	<1
Sexual dysfunction	<1	-
Spotty menstruation	-	<1
Hematological		
Hemolytic anemia	✔	-
Increased bleeding time	✔	-
Leukopenia	✔	-
Purpura	✔	<1
Thrombocytopenia	✔	-
Laboratory Abnormalities		
Alkaline phosphatase increase	≤1	-
Creatine phosphokinase elevation	<1	-
Hepatic enzyme elevations	<1	1.4
Hyperkalemia	-	-
Musculoskeletal		
Arthralgia	-	<1
Extrapyramidal symptoms	✔	-
Gait abnormality	<1	-
Muscle cramps	<1	<1
Myopathy	✔	-
Neck rigidity	<2	-
Paresthesia	-	<1
Osteoarthritis	<1	-
Respiratory		
Cough	2	✔
Dyspnea	<1	1.4
Epistaxis	<1	-
Nasal congestion	<1-2	-
Upper respiratory tract infection	-	5.4
Other		
Abnormal visual accommodation	<1	<1
Allergic reaction	✔	-
Angioedema	✔	-
Edema	2.4-9.0	1.9-3.0
Eye pain	<1	-
Hyperuricemia	<1	-
Peripheral edema	✔	✔
Retinopathy	✔	-
Taste perversion	✔	-
Tinnitus	<1	<1
Weight gain	<1	-

- Event not reported.
✔ Percent not specified.

Contraindications[12-25]

General contraindications of calcium-channel blockers include hypersensitivity to the drug or any components, sick sinus syndrome, second- or third- degree heart block (exception for those with ventricular pacemaker), and

patients suffering from hypotension. Diltiazem is contraindicated in patients with acute myocardial infarction or those with pulmonary congestion documented by x-ray. Verapamil should not be used in patients suffering from severe left ventricular dysfunction, severe heart failure or cardiogenic shock. Additionally, patients with atrial fibrillation or atrial flutter with an accessory bypass tract are not candidates for therapy with verapamil.

Special Precautions of Class[12-25]
Calcium-channel blocking agents such as diltiazem and verapamil should be used with caution in patients with congestive heart failure and impaired hepatic function. Abrupt withdrawal of either agent should be avoided.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous calcium-channel blocking agents are summarized in Table 7.

Table 7. Usual Dosing for the Miscellaneous Calcium-Channel Blocking Agents[12-25]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Diltiazem immediate release (IR)	Chronic Stable Angina: Tablet: initial, 30 mg four times a day; maintenance, 180 to 360 mg daily Vasospastic Angina[#]: Tablet: initial, 30 mg four times a day; maintenance, 180 to 360 mg daily	Safety and efficacy has not been established in pediatric patients.	Injection: 5 mg/mL vial 100 mg vial port Tablet: 30 mg 60 mg 90 mg 120 mg
Diltiazem extended release (ER) (twice daily)	Hypertension: Tablet: initial, 60 to 120 mg twice daily; maintenance, 240 to 360 mg daily	Safety and efficacy has not been established in pediatric patients.	Capsule: 60 mg 90 mg 120 mg
Diltiazem ER (once daily)	Chronic Stable Angina: Capsule: initial, 120 mg; maintenance, 180 to 480 mg daily; maximum, 480 mg daily Chronic Stable Angina (Cardizem LA): Capsule: initial, 180 mg; maintenance, 180 to 360 mg daily Hypertension: Capsule: initial, 180 to 240 mg once daily; maintenance, 180 to 480 mg daily; maximum, 540 mg daily Hypertension (Cardizem LA): Capsule: initial, 180 to 240 mg once daily; maintenance, 180 to 540 mg daily; maximum, 540 mg daily	Safety and efficacy has not been established in pediatric patients.	Capsule: 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg
Verapamil IR	Arrhythmias: Tablet: maintenance, 240 to 320 mg daily divided (three to four times daily) Chronic Stable Angina: Tablet: initial, 40 to 120 mg three times a day; maintenance, 80 to 120 mg three times a day; maximum, 480 mg daily Hypertension:	Safety and efficacy has not been established in pediatric patients.	Tablet: 40 mg 80 mg 120 mg

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 80 mg three times a day; maintenance, 360 to 480 mg daily divided (three to four times daily); maximum, 480 mg daily		
Verapamil ER (once daily)	Hypertension: Tablet: initial, 180 mg once daily; maintenance, 180 to 480 mg daily Chronic Stable Angina: (Covera-HS only) Tablet: maintenance, 180 to 540 mg daily at bedtime	Safety and efficacy has not been established in pediatric patients.	Tablet: 120 mg 180 mg 240 mg Covera-HS tablets: 180 mg 240 mg

[#]Angina due to coronary artery spasm.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous calcium-channel blocking agents are summarized in Table 8.

Table 8. Comparative Clinical Trials for the Miscellaneous Calcium-Channel Blocking Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Angina				
De Rosa et al[47] Diltiazem SR 300 mg QD vs verapamil SR 240 mg QD	DB, XO Men and women, age 48 to 72 years, with stable exertional angina, a positive test for myocardial ischemia and documented coronary artery disease	N=20 12 weeks	Primary: Exercise tolerance test: time to onset of angina, time to 1-mm ST-segment depression and total exercise duration Secondary: Heart rate, angina frequency, nitroglycerin use and adverse events	Primary: Time to onset of angina increased significantly in both groups compared to placebo (verapamil vs placebo; $P<0.05$ and diltiazem vs placebo; $P<0.005$). Time to 1-mm ST-segment depression increased significantly in both groups compared to placebo (verapamil vs placebo; $P<0.05$ and diltiazem vs placebo; $P<0.005$). Total exercise duration increased significantly in both groups compared to placebo (verapamil vs placebo; $P<0.05$ and diltiazem vs placebo; $P<0.005$). For each primary endpoint, there was no significant difference between the treatment groups. Secondary: Heart rates were similar between the treatment groups, except resting heart rate was significantly lower in the diltiazem group as compared to the verapamil group (68.5 vs 75.9; $P<0.05$). Angina frequency and nitroglycerin use decreased significantly in the diltiazem group compared to placebo ($P<0.05$) and to verapamil ($P<0.05$). Edema and flushing were most frequently reported. Similar rates of adverse events were reported for both treatments.
Chugh et al[48] Diltiazem 240 mg QD for	DB, DD, PG, RCT Patients with	N=67 4 weeks	Primary: Treadmill exercise test: time to onset of	Primary: Both treatment groups, and all doses, had significant increases in time to onset of angina from baseline ($P<0.001$ for all). There was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
2 weeks then 360 mg QD for 2 weeks vs amlodipine 5 mg QD for 2 weeks then 10 mg QD for 2 weeks	stable angina, blood pressure in the range of 100/60 mm Hg to 170/110 mm Hg and a positive ischemic response on a treadmill test, history of angiography		angina, time to 1-mm ST-segment depression Secondary: Heart rate, blood pressure, number of angina episodes and use of nitrates	significant difference between the treatment groups (*P*=0.838) and between dose levels (*P*=0.144) in time to onset of angina. Both treatment groups, and all doses, had significant increases in time to 1-mm ST-segment depression from baseline, except low-dose amlodipine (*P*<0.004, except *P*=0.063). There was no significant difference between the treatment groups and between dose levels (*P*=0.114) in time to 1-mm ST-segment depression (*P*=0.691). Secondary: There was no significant difference between the groups in heart rate at rest or maximal exercise. There was no significant difference between the groups in blood pressure at rest or maximal exercise, except SBP at rest was higher in the diltiazem group (137 to 143 vs 129 to 135 mm Hg; *P*=0.029). Both treatments reduced the number of angina episodes and the use of nitrates, but these results were not statistically different between the groups (*P* value not reported).
van Kesteren et al[49] Diltiazem CR 90 to 120 mg BID vs amlodipine 5 to 10 mg QD	DB, MC Men and women, age 41 to 77 years, with a history of stable angina pectoris, a positive exercise tolerance test, and positive thallium scan or positive coronary angiogram	N=132 8 weeks	Primary: Exercise tolerance test: time to 1-mm ST-segment depression, time to onset of chest pain, time to end of exercise (exercise duration) Secondary: Safety	Primary: Diltiazem and amlodipine treatment resulted in significant increases in time to 1-mm ST-segment depression as compared to baseline (*P*<0.0001). Treatments were not significantly different from each other (*P*>0.05). Diltiazem and amlodipine treatment resulted in significant increases in time to onset of chest pain at 4 and 8 weeks, (10% and 13% for amlodipine; *P*<0.0001; 5% and 7% for diltiazem; *P*=0.009). Treatments were not significantly different from each other (*P*>0.05). Amlodipine treatment resulted in a significant increase in total exercise duration as compared to baseline (*P*=0.0002), however the change from baseline for diltiazem was not significantly increased (*P*=0.43). There was no significant difference between the treatment groups at endpoint.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: 10 patients (15.2%) in the amlodipine group and 17 patients (25.8%) in the diltiazem group reported an adverse event; 2 patients from the amlodipine group and 6 patients from the diltiazem group subsequently withdrew from the study.
Frishman et al[50] Diltiazem 240 to 480 mg at bedtime vs amlodipine 5 to 10 mg QD vs amlodipine 5 to 10 mg QD plus atenolol 50 mg QD vs placebo	DB, MC, PC, PG, RCT Patients, age 30 to 80 years, with chronic stable angina pectoris, evidence of exercise-induced ST-segment depression ≥1.0 mm and other evidence of cardiac disease	N=551 4 week	Primary: Exercise tolerance test (symptom-limited exercise duration, time ≥1.0-mm ST-segment depression and time to moderate angina) Secondary: 48-hour Holter-determined number of ischemic episodes, mean and total duration of ischemia, maximal depth of ST depression, heart rate at onset of ischemia	Primary: Treatment with diltiazem, amlodipine, amlodipine plus atenolol resulted in significantly better results than placebo in: symptom-limited exercise duration, time ≥1.0-mm ST-segment depression and time to moderate angina (P≤0.01 for all vs placebo). Secondary: Treatment with diltiazem, amlodipine, amlodipine and atenolol resulted in significantly fewer ischemic episodes in 48-hour Holter monitoring (P=0.003 for verapamil vs placebo). Treatment with amlodipine monotherapy resulted in a significant increase in duration of ischemic episode (P≤0.05 vs verapamil vs amlodipine plus atenolol and vs placebo). Treatment with verapamil and with amlodipine plus atenolol resulted in a decrease in duration of ischemic episodes as compared to amlodipine and placebo (P≤0.05 for each). HR at the onset of ischemic episode was significantly lower in the verapamil group and in the amlodipine plus atenolol group (P≤0.05 vs amlodipine) and higher in the amlodipine group (P≤0.05 vs verapamil, vs amlodipine plus atenolol and vs placebo).
Hypertension				
Wright et al[51] Diltiazem graded-release 360 to 540 mg QD vs	AC, DB, MC, PG, RCT Male and female African Americans, age 18 to 80 years, with	N=268 12 weeks	Primary: Change from baseline in DBP during first 4 hours of awakening as recorded by ambulatory blood pressure monitoring	Primary: Reductions in DBP during the first 4 hours after awakening, and from 6 AM to noon, were significantly greater in the diltiazem group than in the amlodipine group (–13.12 vs –9.65 mm Hg; P=0.0049 and –11.97 vs –8.75 mm Hg; P=0.0019). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
amlodipine 5 to 10 mg QD	hypertension: DBP 85 to 109 mm Hg and SBP <180 mm Hg		Secondary: Changes from baseline in blood pressure, heart rate, rate-pressure product, safety	Reductions in SBP during the first 4 hours after awakening and between 6 AM and noon, were similar between the groups (*P*<0.0768 and *P*<0.9470). Mean 24-hour SBP reductions were significantly greater in the amlodipine group than in the diltiazem group (–14.08 vs –10.64; *P*=0.0022). Reductions in heart rate were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: –4.88 vs 1.77; *P*<0.0001). Reductions in rate-pressure product were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: –1493 vs –881; *P*<0.0008). Safety: 1.5% of the diltiazem group and 2.2% in the amlodipine group discontinued early due to adverse events.
White et al[52] Diltiazem ER 240 to 540 mg at bedtime vs ramipril 5 to 20 mg at bedtime	DB, MC, PG, RCT Men and women, with hypertension: DBP 90 to 110 mm Hg	N=261 10 weeks	Primary: Change in early morning DBP from baseline Secondary: Change in SBP from baseline, heart rate, heart rate × systolic blood pressure product, 24-hour ambulatory monitoring, safety	Primary: Changes in early morning DBP were significantly larger in the diltiazem group than in the ramipril group (–15 vs –8 mm Hg; *P*<0.001). Secondary: Changes in early morning SBP were significantly larger in the diltiazem group than in the ramipril group (–18 vs –13 mm Hg; *P*=0.002). Decreases in heart rate and heart-rate systolic BP product were significantly larger in the diltiazem group than in the ramipril group (–8.9 vs –2.7 beats/min; *P*<0.0001 and –2518 vs –1393; *P*<0.0001). Reductions in DBP and heart rate and increases in the rate-pressure product measured by 24-hour ambulatory monitoring and clinic monitoring were significantly greater for diltiazem than for ramipril (*P*<0.0001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				50% of diltiazem patients and 40% of ramipril patients reported experiencing any adverse event; edema and cough respectively were most frequently reported for each treatment. Withdrawal rates from the study were low and similar between the groups (*P* values not reported).
Rosei et al[53] VHAS Verapamil SR 240 mg QD vs chlorthalidone 25 mg QD	DB (1st 6 months), MC, PG, RCT Males and females, age 40 to 65 years, with hypertension: SBP ≥160 mm Hg and DBP ≥95 mm Hg	N=1,414 2 years	Primary: Blood pressure Secondary: Cardiovascular events, adverse events	Primary: Both treatments significantly reduced SBP and DBP compared to baseline, however reductions did not significantly differ between treatments: verapamil reduction of 27.6/17 mm Hg vs chlorthalidone reduction of 28.6/16.6 mm Hg (*P*<0.01 for each vs baseline). Goal DBP was achieved in 69.3% of patients receiving verapamil and 66.9% of patients receiving chlorthalidone (*P* value not reported). Secondary: Serum total cholesterol levels and heart rate decreased significantly in the verapamil group as compared to baseline and the chlorthalidone treatment group (total cholesterol; *P*<0.01 for both: heart rate; *P*<0.05). The number of nonfatal cardiovascular events was similar between the groups, 37 in the verapamil group and 39 in the chlorthalidone group (*P* value not reported). The number of cardiovascular deaths was similar between the groups, 5 in the verapamil group and 4 in the chlorthalidone group (*P* value not reported). Hypokalemia and hyperuricemia occurred significantly more frequently in the chlorthalidone group than in the verapamil group (*P*<0.01 for both). 236 patients reported 403 adverse events in the chlorthalidone group and 230 patients reported 387 adverse events in the verapamil. Asthenia was the most commonly reported adverse event in the chlorthalidone group and constipation was the most commonly reported adverse event in the verapamil group.
Messerli et al[54]	DB, MC, PC, PG,	N=581	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Verapamil SR 240 mg QD vs trandolapril 4 mg QD vs verapamil SR 240 mg and trandolapril 4 mg QD (separate entities)	RCT Patients, 21 years old and older with DBP of 95 to 114 mm Hg	6 weeks	Blood pressure Secondary: Not reported	All 3 treatment groups had significant blood pressure reductions from baseline (*P*<0.01 for all). Patients receiving the combination of trandolapril and verapamil had significantly greater reductions in blood pressure as compared to patients receiving trandolapril or verapamil alone (*P*<0.01 for both comparisons). Secondary: Not reported
Cardiovascular Outcomes				
Boden et al[55] INTERCEPT Diltiazem 300 mg QD vs placebo QD	DB, MC, PG, PRO, RCT Patients, age 75 years old and younger, with acute myocardial infarction, without congestive heart failure and who received a thrombolytic agent	N=874 Up to 6 months	Primary: Composite first-event rate of: cardiac death, nonfatal reinfarction or refractory ischemia Secondary: Composite of first occurrence of cardiac death, nonfatal reinfarction, recurrent ischemia, composite of cardiac death, nonfatal reinfarction, need for myocardial revascularization, safety	Primary: There was no significant difference between diltiazem treatment and placebo in composite event rate: 131 primary outcome events occurred in the placebo group and 97 occurred in the diltiazem group (*P*=0.07). Secondary: Rates of all composite nonfatal cardiac events (nonfatal reinfarction combined with refractory ischemia or all recurrent ischemia or need for revascularization) significantly favored diltiazem over placebo (*P*=0.05, *P*=0.05, *P*=0.03 respectively). Rates of cardiac death, nonfatal reinfarction, refractory ischemia and all recurrent ischemia were similar between the diltiazem group and the placebo group, however the need for revascularization favored the diltiazem group (*P*=0.67, *P*=0.47, *P*=0.07, *P*=0.07, *P*=0.03). There was no increase in rates of congestive heart failure, bleeding, cancer or cerebrovascular accidents in the diltiazem group.
Gibson et al[56] Diltiazem 60 mg QID or verapamil 120 mg TID	Retrospective combined subgroup analysis of 2 RCT	N=817 12-18 months	Primary: All cause mortality Secondary: Combined cardiac	Primary: Patients receiving treatment (either agent) had a 42% lower mortality rate than those receiving placebo (*P*=0.010). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo	Patients suffering acute non-Q-wave myocardial infarction		events	Patients receiving treatment (either agent) had a 31% lower event rate (death or recurrent myocardial infarction) than those receiving placebo (*P*<0.006).
Pepine et al[57] INVEST Verapamil SR 120 to 480 mg QD vs atenolol 25 to 200 mg QD	MC, open blinded endpoint, PRO, RCT Patients, age 50 years old and older, with hypertension, requiring drug therapy (blood pressure>140/90 mm Hg or >130/80 mm Hg if diabetic or with renal impairment), and documented coronary artery disease	N=22,576 24 months	Primary: First occurrence of combined: death (all-cause), nonfatal myocardial infarction, or nonfatal stroke Secondary: Occurrence of: death (all-cause), nonfatal myocardial infarction, nonfatal stroke; time to most serious event, cardiovascular death, angina, cardiovascular hospitalization, blood pressure control, cancer, Alzheimer disease, Parkinson disease, gastrointestinal tract bleeding, adverse events	Primary: There was no significant difference between the verapamil group and the atenolol group in time to first occurrence of death, nonfatal myocardial infarction and nonfatal stroke (*P*=0.57). 1,171 events were reported by 1,119 patients in the verapamil group and 1,209 events were reported by 1,150 patients in the atenolol group. Secondary: All cause death occurred in 873 patients in the verapamil group and 893 patients in the atenolol group (*P*=0.72). Equal number, 431 in each treatment group was classified as cardiovascular. Nonfatal myocardial infarctions were reported in 151 patients in the verapamil group and 153 patients in the atenolol group (*P*=0.95). Nonfatal strokes were reported in 131 patients in the verapamil group and 148 patients in the atenolol group (*P*=0.33). There was no significant difference between the verapamil group and the atenolol group in cardiovascular related death or hospitalization (*P*=0.94, *P*=0.59). Reported angina decreased similarly in both groups (*P*=0.18), however the average frequency was lower in the verapamil group as compared to the atenolol group (*P*=0.02). There was no significant difference between the verapamil group and the atenolol group in reduction of SBP (verapamil –18.7 vs –19.0 mm Hg; *P*=0.41) and DBP (verapamil –10.0 vs –10.2 mm Hg; *P*=0.26). Overall, 71.7% of verapamil and 70.7% of atenolol patients achieved blood pressure goal at 24 months (*P*=0.18).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				The average resting heart rate was lower in the atenolol group than the verapamil group (69.2 beats/minute vs 72.8 beats/minute; *P*<0.001). Rates did not differ between the groups for rates of cancer, Alzheimer disease, Parkinson disease or gastrointestinal tract bleeding (*P*>0.05 for all). Constipation and cough were reported more frequently with verapamil mil and dyspnea, lightheadedness, symptomatic bradycardia and wheezing were more frequently reported in the atenolol group.
Mancia et al[58] Verapamil SR 120 to 480 mg QD vs atenolol 25 to 200 mg QD	MC, open blinded endpoint, PRO, RCT Patients with hypertension, requiring drug therapy (blood pressure>140/90 mm Hg or >130/80 mm Hg if diabetic or with renal impairment), and coronary artery disease	N=22,576 24 months	Primary: Occurrence of death, nonfatal myocardial infarction and nonfatal stroke Secondary: Blood pressure control rates	Primary: Rates (death, nonfatal myocardial infarction and nonfatal stroke) were similar for both treatment groups (*P* value not reported). Secondary: Rates of death, myocardial infarction and stoke declined as the number of office visits for which blood pressure was controlled increased (*P*<0.001).
Hansson et al[59] NORDIL Diltiazem 180 to 360 mg QD vs conventional (diuretic, β-	Blinded endpoint, MC, open, PRO, RCT Patients, age 50 to 74 years, with DBP ≥100 mm Hg and previously untreated	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, other cardiovascular death Secondary: Fatal plus nonfatal	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/beta-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; *P*=0.97). Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/beta-blocker patients (*P*=0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
blocker or both)			stroke and fatal plus nonfatal myocardial infarction	Fatal plus nonfatal myocardial infarction occurred in 183 of the diltiazem patients and 157 of the diuretic/beta-blocker patients (*P*=0.17). Other endpoints were not statistically different between the groups including: cardiovascular death (*P*=0.41), all cardiac events (*P*=0.57 and congestive heart failure (*P*=0.42).
Black et al[60] CONVINCE Verapamil ER 180 mg QD vs atenolol 50 mg QD vs HCTZ 12.5 mg QD	AC, DB, MC, RCT Patients, age 55 years and older, with hypertension and at least one risk factor for cardiovascular disease	N=16,476 3 years	Primary: Composite: first occurrence of acute myocardial infarction, stroke or cardiovascular disease-related death Secondary: Cardiovascular endpoints expanded, all-cause mortality, cancer, hospitalization for bleeding, incidence of primary endpoints between 6 AM and noon, adverse events	Primary: There was no significant difference between the verapamil treatment group and the atenolol/HCTZ treatment group in the composite primary endpoint (HR, 1.02; 95% CI, 0.88 to 1.18; *P*=0.77). Secondary: There was no significant difference between the verapamil treatment group and the atenolol/HCTZ treatment group in rates of cardiovascular-related hospitalization (*P*=0.31) and death (all-cause mortality) (*P*=0.32), cancer rates (*P*=0.46). Patients treated with verapamil experience a significantly higher rate of death or bleeding unrelated to stroke (HR, 1.54; 95% CI, 1.15 to 2.04; *P*=0.003). Primary endpoints did not differ significantly based on time of day (*P*=0.43). Patients treated with verapamil were more likely to withdraw for adverse events or symptoms than those in the atenolol or HCTZ (*P*=0.02).

Drug regimen abbreviations: BID=twice daily, CR=controlled release, ER=extended release, QD=once daily, QID-four times daily, SR=sustained release, TID=three times a day
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=risk ratio, XO=crossover
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Miscellaneous Calcium-Channel Blocking Agents

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
diltiazem	controlled-release capsule, injection, sustained-release capsule, sustained-release tablet, tablet	Cardizem®*, Cardizem CD®*, Cardizem LA®, Dilacor XR®*, Tiazac®*	$$$-$$$$	$-$$
verapamil	extended-release capsule, injection, sustained-release tablet, tablet	Calan®*, Calan SR®*, Covera-HS®, Isoptin SR®*, Verelan®*, Verelan PM®*	$$$-$$$$	$-$$$

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

X. Conclusions

The miscellaneous calcium-channel blocking agents, diltiazem and verapamil, are Food and Drug Administration (FDA) approved for the treatment of hypertension and some products have additional indications for angina and arrhythmia. Evaluation of the available clinical trials comparing diltiazem and verapamil in the treatment of angina reveals that there is little or no difference in efficacy between the agents.[47] Clinical trials comparing diltiazem to other agents (amlodipine and atenolol) showed that both treatments were effective at increasing exercise tolerance in patients with angina, with no significant differences reported.[48-50]

In the treatment of hypertension, clinical trials have compared diltiazem and verapamil to various comparator agents, including dihydropyridines, other calcium channel blockers such as amlodipine, angiotensin-converting enzyme inhibitors such as ramipril, diuretics such as chlorthalidone, and placebo. The results of these trials show that both diltiazem and verapamil are effective at controlling both systolic and diastolic blood pressure.[51-54] Diltiazem was more effective than amlodipine at controlling early morning diastolic blood pressure in African American patients; however in the same trial there was no difference in effects on systolic blood pressure for early morning measurements, and averages of systolic blood pressures over 24-hours favored amlodipine.[51] In a comparison of diltiazem to ramipril, blood pressure measurements were significantly improved with diltiazem as compared to ramipril.[52] Comparisons of verapamil to chlorthalidone and to trandolapril revealed equally potent reductions in blood pressure.[53,54]

A third category of clinical trials evaluated these agents for the prevention of cardiovascular events, and in the context of these trials, diltiazem and verapamil were shown to be effective options for reducing mortality and event rates as compared to atenolol, hydrochlorothiazide, and placebo.[56-60] However, it should be kept in mind that treatment for cardiovascular disease and prevention of cardiovascular events should be conducted in accordance with the comprehensive evidence-based reviews embodied in national and international guidelines.[26-45] Overall, studies comparing diltiazem directly to verapamil are lacking, only one small study, which is evaluated in this review, directly compared the two agents.[47]

Diltiazem and verapamil are available in generic formulations for regular and sustained/extended release products. Only a single formulation of diltiazem, extended release tablets, Cardizem LA®, is not available as a generic product; however, other long-acting formulations of diltiazem are available as generic capsules. There is one brand of verapamil for which there is no generic equivalent (Covera-HS®), but several other long-acting formulations of verapamil are available.

Therefore, all brand products within the reviewed class are comparable to each other and to the generics products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous calcium-channel blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Angiotensin-Converting Enzyme Inhibitors
Single Entity Agents
AHFS Class 243204
September 10, 2008

I. Overview

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[1,2] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[3] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase).[1] Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[1,3] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including ventricular hypertrophy, remodeling and myocyte apoptosis.[1,2]

The ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator.[4] Evidence-based guidelines recognize the important role that ACE inhibitors play in the treatment of hypertension and other cardiovascular and renal diseases.

The single entity ACE inhibitors included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the ACE inhibitors are available generically with the exception of perindopril.

Table 1. Single Entity Angiotensin-Converting Enzyme (ACE) Inhibitors Included in This Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
benazepril	tablet	Lotensin®*	benazepril
captopril	tablet	Capoten®*	captopril
enalapril	tablet	Vasotec®*	enalapril
enalaprilat dihydrate	injection	Vasotec®*†	enalaprilat dihydrate
fosinopril	tablet	Monopril®*	fosinopril
lisinopril	tablet	Prinivil®*, Zestril®*	lisinopril
moexipril	tablet	Univasc®*	moexipril
perindopril	tablet	Aceon®	Aceon®
quinapril	tablet	Accupril®*	quinapril
ramipril	capsule, tablet	Altace®*	ramipril
trandolapril	tablet	Mavik®*	Mavik®*, trandolapril

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines using the single entity angiotensin-converting enzyme (ACE) inhibitors are summarized in Table 2. For a more comprehensive overview of the pharmacologic treatment of angina pectoris, chronic heart failure, hypertension, and acute myocardial infarction, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Single Entity Angiotensin-Converting Enzyme (ACE) Inhibitors

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina**	• Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including ACE inhibitors and/or β-adrenergic blocking agents (β-blockers) with the addition of other

Clinical Guideline	Recommendation
Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)[5]	medications as needed to achieve blood pressure goals of <140/90 mm Hg or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction of ≤40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal left ventricular ejection fraction in whom cardiovascular risk factors remain well controlled and revascularization has been performed) unless contraindicated.
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[6]	• Inhibitors of the renin-angiotensin-aldosterone system can be used in the acute setting during early hospitalization. • ACE inhibitors should be initiated and continued indefinitely in patients with heart failure, left ventricular dysfunction, diabetes, or hypertension unless contraindicated. Angiotensin receptor blockers (ARBs) should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and signs of heart failure and left ventricular ejection fraction <40%. • ACE inhibitors are reasonable for all patients, even without left ventricular dysfunction, hypertension, or diabetes mellitus unless contraindicated. • ACE inhibitors are reasonable for patients with heart failure and left ventricular ejection fraction <40%. • Patients who cannot tolerate ACE inhibitors may be treated with an ARB if they have signs of heart failure and left ventricular ejection fraction <40%. • Combination ACE inhibitor and ARB therapy may be considered in patients with persistent symptomatic heart failure and left ventricular ejection fraction <40% despite conventional therapy including an ACE inhibitor or ARB alone, unless the patient is already on an aldosterone antagonist. • In patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with chronic kidney disease or diabetes mellitus), it is useful to add blood pressure medication(s) as tolerated, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve target blood pressure.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)**[7]	Therapy to Improve Prognosis • ACE inhibitors should be considered in patients with stable angina and comorbid hypertension, diabetes, heart failure, asymptomatic left ventricular dysfunction, and patients who have had a myocardial infarction. Patients with stable angina who do not have an indication for an ACE inhibitor may be treated with one if the benefits of the agent (possible absolute risk reduction) outweigh the possible side effects. Treatment of Syndrome X • ACE inhibitors are recommended in patients with hypertension.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS) (2007)**[8]	• ACE inhibitors are recommended in all patients with left ventricular ejection fraction ≤40% and in patients with diabetes, chronic kidney disease, and hypertension unless otherwise contraindicated. • ACE inhibitors should be considered for all other patients to prevent the recurrence of ischemia. Agents and doses of proven efficacy are recommended (ramipril and perindopril). • ARBs should be considered in patients intolerant to ACE inhibitors and/or who have heart failure or have had a myocardial infarction with a left ventricular ejection fraction of ≤40%.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic**	Symptomatic Patients • The following agents are recommended to prevent myocardial infarction or death and to reduce symptoms: aspirin (clopidogrel may be used in patients intolerant to aspirin), β-blockers, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), and ACE inhibitors.

Clinical Guideline	Recommendation
Suspected or Known Coronary Artery Disease (2004)[9]	Asymptomatic Patients With Evidence Suggesting CAD on Previous Testing • The following agents should be used to prevent myocardial infarction and death: aspirin (in patients with a previous myocardial infarction), β-blockers (in patients with a previous myocardial infarction), statins (in patients with type 2 diabetes or documented CAD), and an ACE inhibitor (in patients with documented CAD and diabetes, systolic dysfunction, or both). • The following agents may also be used to prevent myocardial infarction and death: aspirin in patients who have not had a previous myocardial infarction, and an ACE inhibitor in patients with diabetes and no contraindications.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[10]	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors, and β-blockers have been shown to prevent heart failure. The ARBs losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes mellitus and nephropathy. • Lipid disorders should be treated according to contemporary guidelines. • ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, myocardial infarction, and heart failure. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left ventricular dysfunction or hypertension. • ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes, and hypertension with other cardiovascular risk factors. Patients With Cardiac Structural Abnormalities or Remodeling Who Have not Developed Heart Failure Symptoms (Stage B) • β-Blockers and ACE inhibitors should be used in all patients with a recent or past history of myocardial infarction. • β-Blockers and ACE inhibitors should be used in patients who have reduced left ventricular ejection fraction and do not have a history of myocardial infarction or heart failure. • ARBs are recommended for patients with reduced left ventricular ejection fraction and a history of a myocardial infarction if they are intolerant to ACE inhibitors. • ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • ACE inhibitors are recommended in all patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated. • ARBs approved for the treatment of heart failure are recommended in all patients intolerant to ACE inhibitors with current or past symptoms of heart failure and reduced left ventricular ejection fraction. • ARBs are reasonable alternatives to ACE inhibitors as first-line therapy in patients with mild-to-moderate heart failure and reduced left ventricular ejection fraction. • The addition of an ARB is reasonable in patients who are symptomatic despite conventional treatment. • The routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

Clinical Guideline	Recommendation
	• β-Blockers, ARBs, ACE inhibitors, and calcium-channel blocking agents (CCBs) may be useful in patients with heart failure and controlled hypertension to improve symptoms.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[11]	<u>Patients at Risk for Development of Heart Failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure, including patients with CAD, peripheral vascular disease, stroke, diabetes plus another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction</u> • ACE inhibitors are recommended. ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of ACE inhibitors and ARBs together is not recommended. <u>Patients With Left Ventricular Systolic Dysfunction</u> • ACE inhibitors should be used in all patients with a left ventricular ejection fraction ≤40% unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a left ventricular ejection fraction ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a myocardial infarction and have left ventricular dysfunction is not recommended. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a myocardial infarction and in patients with chronic heart failure and systolic dysfunction. <u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least 1 other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. <u>Patients With Heart Failure and Coronary Artery Disease</u> • ACE inhibitors are recommended after a myocardial infarction. • ACE inhibitor and β-blocker therapy should be initiated early (within 48 hours) in hospitalized stable patients who have had a myocardial infarction and have left ventricular dysfunction. <u>Managing Patients With Heart Failure and Hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or CCB. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent. • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target

Clinical Guideline	Recommendation
	doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non–cardiac-depressing CCB (amlodipine) may be considered. <u>Managing Heart Failure in the Elderly, Women, and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)**[12]	• ACE inhibitors are recommended in patients with left ventricular ejection fraction 40% to 45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention. • ARBs may be used in patients who are intolerant to ACE inhibitor therapy. They may also be used in combination with ACE inhibitors in patients who remain symptomatic.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)**[13]	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • In patients with acute coronary syndromes (myocardial infarction or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. • For patients with post-myocardial infarction, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients. • ACE inhibitors and ARBs should not be given to women who are pregnant or may

Clinical Guideline	Recommendation
	become pregnant. • ACE inhibitors should not be used in patients who have a history of angioedema.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[14]	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics, dihydropyridine CCBs), renal disease (ACE inhibitors, ARBs), post-myocardial infarction (ACE inhibitors, β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics, ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[15]	• The choice of drug should depend on several factors, including previous patient response to a class of medications, the effect of a medication on cardiovascular risk according to the patient's cardiovascular profile, presence of compelling indications for certain medications, the presence of disorders which may limit the use of a class of medications, possibility of drug interactions, and side effects. • Drugs which exert their effects for 24 hours and can be given once daily should be preferred to enhance compliance. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors, ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end-stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[16]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[17]	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • Initial therapy in patients younger than 55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[18]	<u>General Recommendations</u> • If ACE inhibitors, ARBs or diuretics are used, kidney function and serum potassium levels should be closely monitored. • ACE inhibitors and ARBs are contraindicated during pregnancy. <u>Hypertension</u>

Clinical Guideline	Recommendation

	• Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate (GFR) is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated GFR is <50 mL/min/1.73 m^2.
	
	<u>Coronary Heart Disease</u>
	• In patients with known cardiovascular disease and in patients >40 years with another cardiovascular risk factor, ACE inhibitor, aspirin, and statin therapy (if not contraindicated) should be used to reduce the risk of cardiovascular events.
	
	<u>Diabetic Nephropathy</u>
	• In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used.
	• While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements:
	  • In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy.
	  • In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBS have been shown to delay the progression to macroalbuminuria.
	  • In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy.
	  • If one class is not tolerated, the other should be substituted.

International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[19]	• All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy. • CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • African American patients appear to be at an increased risk for ACE inhibitor-associated cough, angioedema, or both. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[20]	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-myocardial infarction with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-myocardial infarction (β-blockers), chronic stable angina (CCBs, β-blockers), high CAD risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), and supraventricular tachycardia (β-blockers, nondihydropyridine CCBs).

Clinical Guideline	Recommendation
	• Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)**[21]	Secondary Prevention • Patients with comorbid hypertension should be treated initially with β-blockers and/or ACE inhibitors with the addition of other medications as needed to achieve a blood pressure goal of <140/90 mm Hg (or <130/80 mm Hg in patients with diabetes or chronic kidney disease). • ACE inhibitors are recommended in all patients with a left ventricular ejection fraction ≤40% and those with hypertension, diabetes, or chronic kidney disease unless contraindicated. • ACE inhibitors are reasonable in patients with normal left ventricular function and well-controlled cardiovascular risk factors. • ARBs are recommended in patients who are intolerant to ACE inhibitors and have heart failure or who have a left ventricular ejection fraction of ≤40%. • ARBs should be considered in all patients intolerant to ACE inhibitor therapy. • Combination therapy with ARBs and ACE inhibitors may be considered in patients with systolic dysfunction heart failure.
National Institute for Health and Clinical Excellence (NICE): **Post-Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)**[22]	• An ACE inhibitor is recommended for all patients who have had a myocardial infarction. • ACE inhibitors are recommended early after presentation with an acute myocardial infarction. • ARBs are recommended in patients who are intolerant to ACE inhibitor therapy. • Combination therapy with an ACE inhibitor and an ARB is not routinely recommended. • In patients with a proven myocardial infarction in the past and with heart failure and left ventricular systolic failure, treatment should be in line with recommendations for chronic heart failure. • In patients with a proven myocardial infarction in the past and with asymptomatic left ventricular systolic dysfunction and in those without heart failure and preserved left ventricular function, ACE inhibitors are recommended (ARBs may be given to patients who are intolerant of ACE inhibitors).
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)**[23]	Prophylactic Therapies in the Acute Phase • ACE inhibitor should be initiated within 24 hours. Secondary Prevention • ACE inhibitors should be continued unless contraindicated.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the single entity angiotensin-converting enzyme (ACE) inhibitors are outlined 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 Single Entity Angiotensin-Converting Enzyme (ACE) Inhibitors[24-35]

Indication	Benazepril	Captopril	Enalapril/ Enalaprilat	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Acute myocardial infarction to improve survival					✔					
Asymptomatic left ventricular dysfunction			✔							
Diabetic nephropathy		✔								
Heart failure		✔	✔	✔	✔			✔	✔ *	✔ *
Hypertension	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Left ventricular dysfunction		✔ *								✔ *
Stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction							✔			
Reduce risk of myocardial infarction, stroke, and death from cardiovascular causes									✔	

*Post-myocardial infarction.

IV. Pharmacokinetics

Table 4 outlines important pharmacokinetic properties of the single entity angiotensin-converting enzyme (ACE) inhibitors. All of the ACE inhibitors are prodrugs, with the exception of captopril and lisinopril.[36] Captopril and moexipril should be taken 1 hour before meals since food significantly reduces their absorption.

Table 4. Pharmacokinetic Parameters of the Single Entity Angiotensin-Converting Enzyme (ACE) Inhibitors[24-36]

Drug	Bioavailability (%)	Protein Binding (%)	Elimination	Active Metabolites	Half-Life (hours)
Benazepril	≥37	~96*	Renal (20%)***,** bile (11%-12%)*****	Yes, benazeprilat	10-11*
Captopril	≥75	~25-30	Renal (>95%)	None	<2
Enalapril	~60	50-60	Renal (60%-80%), feces	Yes, enalaprilat	11*
Enalaprilat	No data	No data	Renal (>90%)	None	35-38
Fosinopril	~36	~ 100*	Renal (50%), feces (50%)	Yes, fosinoprilat	12*
Lisinopril	~25	None	Renal (100%)	None	12
Moexipril	~13	~50*	Feces (53%), renal (13%)	Yes, moexiprilat	2-9*
Perindopril	~75	60 (10-20)*	Renal	Yes, perindoprilat	1 (3-10)*
Quinapril	≥60	~97	Renal	Yes, quinaprilat	2*
Ramipril	≥50-60	73 (56)*	Renal (60%), feces (40%)	Yes, ramiprilat	9-18*
Trandolapril	10 (70)*	80	Feces (66%), renal (33%)	Yes, trandolaprilat	6 (10)*

*Active metabolite.

V. Drug Interactions

Significant drug interactions with the single entity angiotensin-converting enzyme (ACE) inhibitors are listed in Table 5.

Table 5. Significant Drug-Drug Interactions for the Single Entity Angiotensin-Converting Enzyme (ACE) Inhibitors[36]

Drug(s)	Significance Level	Interaction	Mechanism
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	2	Indomethacin	Indomethacin inhibits prostaglandin synthesis. The hypotensive effect of ACE inhibitors may be reduced.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, trandolapril)	2	Lithium	Through an unknown mechanism, ACE inhibitors may increase lithium levels, which results in neurotoxicity.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	1	Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	Combining ACE inhibitors and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high-risk patients (e.g., renal impairment).
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	2	Salicylates (aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate)	Salicylates inhibit prostaglandin synthesis. The hypotensive and vasodilator effects of the ACE inhibitor may be reduced.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	ACE inhibitors may temporarily increase insulin sensitivity and increase the risk of hypoglycemia.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the single entity angiotensin-converting enzyme (ACE) inhibitors are noted in Table 6. The black box warning regarding the use of ACE inhibitors during pregnancy is summarized in Table 7.

Table 6. Adverse Reactions (%) Reported with the Single Entity Angiotensin-Converting Enzyme (ACE) Inhibitors [36]

Adverse Event	Benazepril	Captopril	Enalapril/ Enalaprilat	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandol-april
Cardiovascular										
Angina	<1	0.2-0.3	1.5	0.2-1.0	-	<1	-	<0.5	<1-3	-
Bradycardia	-	-	0.5-1.0	0.4-1.0	0.3-1.0	-	-	-	<1	0.3-4.7
Cardiac arrest	-	✔	0.5-1.0	✔	0.3-1.0	-	✔	-	✔	-
Cerebrovascular accident	-	✔	0.5-1.0	0.2-1	0.3-1.0	<1	0.2	<0.5	<1	-
Chest pain	-	1	2.1	0.2-2.2	3.4	>1	2.4	2.4	<1	0.3-1.0
Hypotension	0.3	✔	0.9-6.7	0.2-4.4	1.2-9.7	0.5	0.3-1.0	2.9	0.5-1.01	0.3-1.1
Myocardial infarction	-	0.2-0.3	0.5-1.0.2	0.2-1.0	0.3-1.0	<1	0.3-1.0	<0.5	<1	-
Orthostatic hypotension	0.4	✔	1.2-2.2	≤1.2-1.9	0.3-1.2	0.51	0.3-1.0	<0.5	2	-
Palpitations	<1	1	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.9-1.1	0.5-1.0	<1	0.3-1.0
Peripheral edema	<1	-	-	-	0.3-1.0	>1	-	-	-	-
Rhythm disturbances	-	✔	0.5-1.0	≤ 0.2-1.4	-	<1	-	<0.5	-	-
Tachycardia	-	1	0.5-1.0	0.4-1	0.3-1.0	-	-	0.5-1.0	<1	-
Central Nervous System										
Anxiety	<1	-	-	-	-	<1	0.3-1.0	-	<1	0.3-1.0
Ataxia	-	✔	0.5-1.0	-	0.3-1.0	-	-	-	-	-
Depression	-	✔	0.5-1.0	0.4-1	-	-	2	0.5-1.0	<1	-
Dizziness	3.6	-	0.5-7.9	1.6-11.9	5.4-11.8	4.3	8.2	3.9-7.7	1.9-4	1.3-23
Fatigue	2.4	-	0.5-3	≥1	2.5	2.4	-	2.6	2	-
Headache	6.2	-	1.8-5.2	≥1	4.4-5.7	>1	23.8	1.7	-	-
Insomnia	<1	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	2.5	0.5-1.0	<1	0.3-1.0
Malaise	-	-	-	-	0.3-1.0	<1	0.3-1.0	0.5-1.0	<1	-
Nervousness	<1	✔	0.5-1.0	-	0.3-1.0	<1	1.1	0.5-1.0	<1	-
Paresthesias	<1	-	0.5-1.0	0.2-1.0	0.3-1.0	-	2.3	0.5-1.0	<1	0.3-1.0
Peripheral edema	<1	-	-	-	-	>1	-	-	-	-
Somnolence/ drowsiness	1.6	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	1.3	0.5-1.0	<1	0.3-1.0

Adverse Event	Benazepril	Captopril	Enalapril/ Enalaprilat	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandol-april
Vertigo	-	-	1.6	0.2-1.0	0.2	-	0.3-1.0	0.5-1.0	<1-2	0.3-1.0
Dermatologic										
Alopecia	<1	-	0.5-1.0	-	0.3-1.0	<1	-	0.5-1.0	-	-
Diaphoresis	<1	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.3-1.0	0.5-1.0	<1	-
Erythema multiforme	-	✔	0.5-1.0	-	-	-	0.3-1.0	-	<1	-
Exfoliative dermatitis	-	✔	0.5-1.0	✔	-	-	✔	<0.5	-	-
Flushing	<1	0.2-0.5	0.5-1.0	0.2-1.0	0.3-1.0	1.6	-	-	-	0.3-1.0
Pemphigus/ pemphigoid	<1	✔	0.5-1.0	-	0.3-1.0	-	-	0.5-1.0	-	0.3-1.0
Photosensitivity	<1	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	-	<0.5	-	-
Pruritus	<1	2	0.5-1.0	0.2-1.0	-	<1	0.3-1.0	0.5-1.0	<1	0.3-1.0
Rash	<1	4-7	0.5-1.0.4	0.2-1.0	0.01-1.7	1.6	2.3	1.4	<1	0.3-1.0
Stevens-Johnson syndrome	<1	✔	0.5-1.0	-	rare	-	-	-	<1	-
Toxic epidermal necrolysis	-	-	0.5-1.0	-	rare	-	-	-	<1	-
Urticaria	-	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	-	<1	<1	-
Gastrointestinal										
Abdominal pain	-	-	1.6	0.2-1.0	2.2	<1	2.7	1	<1	0.3-1.0
Anorexia	-	-	0.5-1.0	-	-	-	-	-	<1	-
Constipation	<1	-	0.5-1.0	0.2-1	0.3-1.0	<1	0.3-1.0	0.5-1.0	<1	0.3-1.0
Diarrhea	-	-	1.4-2.1	>1	2.7-3.7	3.1	4.3	1.7	≤1	0.3-1.0
Dry mouth	-	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.3-1.0	0.5-1.0	<1	-
Dysgeusia	-	2-4	-	-	-	-	-	-	-	-
Dyspepsia	-	✔	0.5-1.0	-	0.3-1.0	>1	0.3-1.0.9	<0.5	<1	0.3-6.4
Hepatitis	-	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	-	<0.5	<1	-
Nausea	1.3	-	1.3-1.4	1.2-2.2	2	>1	2.3	2.4	2	-
Pancreatitis	<1	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	✔	<0.5	<1	0.3-1.0
Vomiting	<1	-	1.3	1.2-2.2	0.3-1.0.1	<1	1.5	2.4	2	0.3-1.0
Genitourinary										
Decreased libido	<1	-	-	0.2-1.0	0.4	-	-	-	-	0.3-1.0
Impotence	<1	✔	0.5-1.0	-	1	-	-	0.5-1.0	<1	0.3-1.0
Oliguria	-	0.1-0.2	0.5-1.0	-	0.3-1.0	<1	-	-	-	-
Urinary tract infection	<1	-	1.3	-	0.3-1.0	-	2.8	0.5-1.0	-	-

Adverse Event	Benazepril	Captopril	Enalapril/ Enalaprilat	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandol-april
Musculoskeletal										
Arthralgia	<1	✔	✔	0.2-1	0.3-1.0	<1	0.3-1.0	0.5-1.0	<1	-
Arthritis	<1	-	✔	✔	0.3-1.0	-	1	-	<1	-
Muscle cramps	-	-	0.5-1.0	0.2-1	0.5	-	-	-	-	0.3-1.0
Myalgia	<1	✔	✔	0.2-1	0.3-1.0	1.3	0.3-1.0.1	-	<1	4.7
Respiratory										
Asthma	<1	✔	0.5-1.0	-	0.3-1.0	-	-	-	-	-
Bronchitis	<1	-	1.3	-	0.3-1.0	-	0.3-1.0	-	-	-
Bronchospasm	-	✔	0.5-1.0	0.2-1	0.3-1.0	<1	-	-	-	-
Cough	1.2	0.5-2	1.3-2.2	2.2-9.7	0.5-3.5	6.1	6-12	2.0-4.3	8	1.9-35
Dyspnea	<1	-	1.3	≥1	0.3-1.0	<1	0.3-1.0	-	<1	0.3-1.0
Pharyngitis	-	-	-	0.2-1	0.3-1.0	1.8	3.3	0.5-1.0	-	-
Rhinitis	-	✔	-	0.2-1	0.3-1.0	>1	4.8	-	-	-
Sinusitis	<1	-	-	0.2-1	0.3-1.0	>1	0.6-5.2	-	-	-
Upper respiratory tract infection	-	-	0.5-1.0	2.2	1.5-2.1	>1	8.6	-	✔	0.3-1.0
Miscellaneous										
Anemia	✔	≤0.2	-	✔	0.3-1.0	<1	-	<0.5	<1	-
Angioedema	0.5	0.1	✔	0.2-1	0.1	<1	0.1	0.1	0.3	0.1
Asthenia	<1	✔	1.1-1.6	-	1.3	-	7.9	-	2	3.3
Blurred vision	-	✔	0.5-1.0	-	0.3-1.0	-	-	-	-	-
Eosinophilia	-	✔	✔	✔	0.3-1.0	-	-	-	<1	-
Fever	-	✔	0.5-1.0	0.4-1	0.3-1.0	-	0.3-1.0.5	-	<1	-
Syncope	0.1	✔	0.5-2.2	0.2-1	0.3-1.8	0.5	0.3-1.0	0.5-1.0	<1-2	5.9
Tinnitus	-	-	0.5-1.0	0.2-1	0.3-1.0	<1	1.5	-	<1	-
Vasculitis	-	✔	✔	-	0.3-1.0	-	✔	-	<1	-

- Event not reported or incidence <1%.
✔ Percent not specified.

Table 7. Black Box Warning for Angiotensin-Converting Enzyme (ACE) Inhibitors and Use in Pregnancy[24-35]

Warning for Use in Pregnancy
CONTRAINDICATION When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, the ACE inhibitor should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

VII. Dosing and Administration

The usual dosing regimens for the single entity angiotensin-converting enzyme (ACE) inhibitors are summarized in Table 8.

Table 8. Usual Dosing for the Single Entity Angiotensin-Converting Enzyme (ACE) Inhibitors[24-35]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Benazepril	Hypertension: Initial, 10 mg once daily (for patients not receiving diuretics); maintenance: 20 to 40 mg per day as a single dose or in 2 equally divided doses; total daily doses above 80 mg have not been evaluated	Hypertension: Children ≥6 years: initial, 0.2 mg/kg once daily; doses above 0.6 mg/kg (or in excess of 40 mg daily) have not been studied. Note: the package insert contains information on how to compound a suspension from the tablets.	Tablet: 5 mg 10 mg 20 mg 40 mg
Captopril	Diabetic nephropathy: Long-term use, 25 mg 3 times a day Heart failure: Initial, 25 mg 3 times a day; maximum: 450 mg daily Hypertension: Initial, 25 mg 2 to 3 times per day; after 1 to 2 weeks, can increase to 50 mg 2 to 3 times per day; maximum: 450 mg daily Left ventricular dysfunction after myocardial infarction: Initial (as early as 3 days following a myocardial infarction), single dose of 6.25 mg then 12.5 mg 3 times a day; target maintenance: 50 mg 3 times a day	Safety and efficacy in children have not been established.	Tablet: 12.5 mg 25 mg 50 mg 100 mg
Enalapril	Asymptomatic left ventricular dysfunction: Initial, 2.5 mg 2 times a day; target maintenance: 20 mg in divided doses Heart failure: Initial, 2.5 mg; maintenance: 2.5 to 20 mg 2 times a day; maximum: 40 mg daily in divided doses Hypertension: Initial, 5 mg once daily (for patients not receiving diuretics); maintenance: 10 to 40 mg per day as a single dose or in 2 divided doses	Hypertension: Initial, 0.08 mg/kg (up to 5 mg) once daily; doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied Note: the package insert contains information on how to compound a suspension from the tablets.	Tablet: 2.5 mg 5 mg 10 mg 20 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Enalaprilat	Hypertension: Initial, 1.25 mg/dose (0.625 mg for patients on diuretics), given over 5 minutes every 6 hours; doses as high as 5 mg every 6 hours have been tolerated for up to 36 hours	Safety and efficacy in children have not been established.	Injection: 1.25 mg/mL
Fosinopril	Heart failure: Initial, 10 mg once daily; maintenance: 20 to 40 mg daily; maximum: 40 mg once daily Hypertension: Initial, 10 mg once daily; maintenance: 20 to 40 mg daily (single or divided doses); maximum: 80 mg daily	Hypertension: Children weighing >50 kg, 5 to 10 mg once daily as monotherapy	Tablet: 10 mg 20 mg 40 mg
Lisinopril	Acute myocardial infarction: Initial, 5 mg every 24 hours for 2 doses (2.5 mg if systolic blood pressure ≤120 mm Hg) then 10 mg every day for 6 weeks (5 mg if systolic blood pressure ≤100 mm Hg with temporary reductions to 2.5 mg if needed) Heart failure: Initial, 5 mg once daily; maintenance: 5 to 20 mg once daily Hypertension: Initial, 10 mg once daily (for patients not receiving diuretics); maintenance: 20 to 40 mg once daily	Hypertension: Children ≥6 years: initial, 0.07 mg/kg (up to 5 mg) once daily; doses >0.61 mg/kg (or in excess of 40 mg) have not been studied Note: the package insert contains information on how to compound a suspension from the tablets.	Tablet: 2.5 mg 5 mg 10 mg 20 mg 30 mg 40 mg
Moexipril	Hypertension: Initial, 7.5 mg once daily (for patients not receiving diuretics); maintenance: 7.5 to 30 mg daily, administered in one or two divided doses; maximum: 60 mg per day	Safety and efficacy in children have not been established.	Tablet: 7.5 mg 15 mg
Perindopril	Hypertension: Initial, 4 mg once daily (for patients not receiving diuretics); maintenance: 4 to 8 mg daily as a single or divided dose; maximum: 16 mg per day Stable coronary artery disease: Initial, 4 mg once daily for 2 weeks; increase as tolerated to 8 mg once daily	Safety and efficacy in children have not been established.	Tablet: 2 mg 4 mg 8 mg
Quinapril	Heart failure: Initial, 5 mg twice daily; titrate at weekly intervals to 10 to 20 mg 2 times a day Hypertension: Initial, Start with 10 to 20 mg once daily (for patients not taking diuretics); titrate at intervals of at least 2 weeks; maintenance: 20 to 80 mg per day in single or 2 equally divided doses	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Ramipril	Heart failure after myocardial infarction: Initial, 2.5 mg twice daily; if hypotensive at this dose, may switch to 1.25 mg twice daily, and after 1 week at the starting dose, titrate toward a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart Hypertension: Initial, 2.5 mg once daily (in patients not receiving diuretics); maintenance: 2.5 to 20 mg per day in single or 2 equally divided doses Reduce risk of myocardial infarction, stroke, and death from cardiovascular causes: Initial, 2.5 mg once daily for 1 week, then 5 mg once daily for the next 3 weeks, and then increase as tolerated to a maintenance dose of 10 mg once daily (dose may be divided if hypertensive or recent myocardial infarction)	Safety and efficacy in children have not been established.	Capsule: 1.25 mg 2.5 mg 5 mg 10 mg Tablet: 1.25 mg 2.5 mg 5 mg 10 mg
Trandolapril	Heart failure or left ventricular dysfunction after myocardial infarction: Initial, 1 mg once daily; titrate as tolerated to target of 4 mg once daily Hypertension: Initial, 1 mg once daily in non-African American patients and 2 mg once daily in African American patients (in patients not receiving diuretics); titrate dose at 1-week intervals; maintenance: 2 to 4 mg once daily (can give twice daily if blood pressure is not controlled with 4 mg once daily); little clinical experience with doses above 8 mg	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 4 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity angiotensin-converting enzyme (ACE) inhibitors are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Single Entity Angiotensin-Converting Enzyme (ACE) Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Coronary Artery Disease				
Swedberg et al[37] CONSENSUS II Enalapril 5 to 20 mg/day vs placebo Treatment was started with an intravenous infusion of 1mg of enalaprilat administered over 3 hours followed by oral enalapril 6 hours after the infusion was stopped.	DB, MC, PC, PG, RCT Patients (mean age 66 years) who presented within 24 hours of the onset of acute myocardial infarction symptoms	N=6,090 180 days	Primary: Mortality rates within 6 months Secondary: Mortality within 1 month, cause of death, re-infarction, or worsening heart failure	Primary: Mortality rates according to life-table analysis between the enalapril and placebo groups at 6 months were not significantly different (11.0% vs 10.2%; *P*=0.26). The relative risk associated with enalapril treatment and based on the mortality curves was 1.10 (95% CI, 0.93 to 1.29). Secondary: Mortality rates between the enalapril and placebo groups at 1 month were not significantly different (7.2% vs 6.3%; *P*=0.26). Death due to progressive heart failure occurred more frequently in patients treated with enalapril than placebo (4.3% vs 3.4%; *P*=0.06). There were no significant differences in the rate of reinfarction between the enalapril or placebo groups (*P*=NS). Change in therapy because of heart failure occurred more in the placebo group (*P*< 0.006) but there were no significant differences in hospitalization for heart failure (*P*=NS). Note: The first CONSENSUS trial excluded patients with a recent myocardial infarction or unstable angina. The study was stopped early after recruiting 6,090 of the intended 9,000 patients since more patients had died on the drug than on placebo (although the difference was not statistically significant).
Fox et al[38] EUROPA Perindopril 8 mg QD	DB, MC, PC, RCT Men and women ≥18 years old (mean age 60	N=12,218 4.2 years (mean)	Primary: Composite of cardiovascular death, myocardial infarction, or cardiac arrest	Primary: Patients treated with perindopril had a significant reduction in the primary outcome compared to patients treated with placebo (8% vs 10%; RR reduction, 20%; 95% CI, 9% to 29%; *P*=0.0003). The benefit began to appear at 1 year and gradually increased throughout the trial.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	years) without clinical heart failure or uncontrolled hypertension with stable CAD and evidence of CHD (eg, myocardial infarction >3 months before screening, percutaneous or surgical coronary revascularization >6 months before screening, 70% narrowing of 1 or more major coronary arteries, history of chest pain)		Secondary: Composite of total mortality, nonfatal myocardial infarction, hospital admission for unstable angina, and cardiac arrest with successful resuscitation; cardiovascular mortality and nonfatal myocardial infarction; individual components of the secondary outcomes and revascularization, stroke, and admission for heart failure	Secondary: Compared with placebo, treatment with perindopril was associated with reductions in all secondary end points. However, not all changes were significant. There was a 14% reduction in total mortality, nonfatal myocardial infarction, unstable angina, and cardiac arrest (*P*=0.0009). There was a 22% reduction in nonfatal myocardial infarction with perindopril (*P*=0.001). Total mortality was 11% lower with perindopril but this finding was not significant (*P*=0.1). Hospital admission for heart failure was significantly reduced with perindopril by 39% (*P*=0.002).
PREAMI Investigators[39] Perindopril 8 mg/day vs placebo	DB, MC, PC, PG, RCT Patients ≥65 years with LVEF ≥40% and recent acute myocardial infarction	N=1,252 12 months	Primary: Composite of death, hospitalization for heart failure or left ventricular remodeling Secondary: Cardiovascular death, hospitalization for reinfarction or angina, revascularization	Primary: The primary end point occurred in 35% of patients taking perindopril and 57% of patients on placebo, with a significant absolute risk reduction of 0.22 (95% CI, 0.16 to 0.28; *P*<0.001). A total of 126 patients (28%) and 226 patients (51%) in the perindopril and placebo groups, respectively, experienced remodeling (*P*<0.001). The mean increase in left ventricular end-diastolic volume was 0.7 mL with perindopril compared with 4.0 mL with placebo (*P*<0.001). Secondary: Cardiovascular death, hospitalization for subsequent acute myocardial infarction or angina or revascularization was infrequent and not modified by treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Conclusion: Perindopril treatment for 1 year reduced progressive left ventricular remodeling but was not associated with better clinical outcomes.
PROGRESS[40] Perindopril (4 mg/day) vs perindopril (4 mg/day) and indapamide (2.5 mg/day or 2.0 mg/day in Japan) vs placebo	DB, MC, PC, RCT Patients with an average age of 64 years with a history of prior stroke or TIA within the previous 5 years	N=6,105 4 years	Primary: Fatal or nonfatal stroke Secondary: Fatal or disabling stroke, total major vascular events comprising the composite of nonfatal stroke, nonfatal myocardial infarction, or death due to any vascular cause (including unexplained sudden death); total and cause specific deaths; hospital admissions	Primary: Patients receiving active treatment experienced a 28% reduction in nonfatal or fatal stroke (95% CI, 17% to 38%; *P*<0.0001). There were similar reductions in the risk of stroke in hypertensive and nonhypertensive subgroups (32% vs 27%; *P*<0.01) A trend towards a greater effect of active treatment among patients treated with combination therapy (43% risk reduction) than in those treated with single drug therapy (5% risk reduction) was reported (no *P* value reported for this comparison). Secondary: There was a 33% reduction in fatal or disabling strokes in the active treatment group (*P* value not specified). Active treatment reduced the risk of total major vascular events by 26% (*P*=0.02). There were no significant differences between active treatment and placebo in total deaths from vascular or nonvascular causes (*P* value not specified). Among those assigned active treatment, there was a 9% RR reduction in hospitalization, with a median reduction of 2.5 days in the time spent in the hospital during follow-up (*P* value not specified). Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. Single drug therapy reduced blood pressure by 5/3 mm Hg and produced no discernable reduction in the risk of stroke.
HOPE Investigators[41] Ramipril 10 mg QD	DB, RCT, two-by-two factorial trial	N=9,297 5 years	Primary: Composite of death from cardiovascular	Primary: Fewer patients on ramipril than placebo (14.0% vs 17.8%, respectively) died of cardiovascular causes or had a myocardial infarction or stroke (RR, 0.78;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Note: the trial also evaluated vitamin E but those results were not included in this review.	Men and women ≥55 years old with history of CAD, stroke, PVD, or diabetes and at least one other cardiovascular risk factor and who were not known to have a low ejection fraction (<40%) or heart failure	(mean)	causes, myocardial infarction, or stroke and each outcome separately Secondary: Death from any cause, revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes Other end points: Worsening angina, cardiac arrest, heart failure, unstable angina with ECG changes, and the development of diabetes	95% CI, 0.70 to 0.86; *P*<0.001). Treatment with ramipril reduced the rates of death from cardiovascular causes (RR, 0.74; *P*<0.001), myocardial infarction (RR, 0.80; *P*<0.001), and stroke (RR, 0.68; *P*<0.001). Secondary: The risk of death from any cause was also significantly reduced by treatment with ramipril (RR, 0.84; *P*=0.005). Significantly fewer patients treated with ramipril underwent revascularization compared with placebo (RR, 0.85; *P*=0.002). Fewer hospitalizations for heart failure were reported with ramipril vs placebo but the risk reduction was not statistically significant (RR, 0.88; *P*=0.25). Fewer complications related to diabetes were reported in patients receiving ramipril (RR, 0.84; *P*=0.03). Other end points: Significantly fewer patients treated with ramipril than placebo group had the following: worsening angina (RR, 0.89; *P*=0.004), cardiac arrest (RR, 0.62; *P*=0.02), heart failure (RR 0.77; *P*<0.001), and new diagnosis of diabetes (RR, 0.66; *P*<0.001). There was no difference between treatment groups for unstable angina with ECG changes (RR, 0.97; *P*=0.76). Note: Patients were excluded if they had heart failure or were known to have a low ejection fraction (< 40%).
ONTARGET Investigators[42] Ramipril 10 mg/day vs telmisartan 80 mg/day	DB, MC, PC, RCT Men and women (mean age 66.4 years in the ramipril and telmisartan arms	N=25,620 56 months (median follow-up)	Primary: Death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure	Primary: The primary outcome occurred in 16.5%, 16.7% and 16.3% of patients receiving ramipril, telmisartan and combination therapy, respectively (*P* values not reported). Secondary: The composite of death from cardiovascular causes, myocardial infarction or stroke occurred in 14.1% of patients in the ramipril group and 13.9% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ramipril 10 mg/day and telmisartan 80 mg/day	and 66.5 years in the combination arm) with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage		Secondary: Composite of death from cardiovascular causes, myocardial infarction or stroke; heart failure, worsening or new angina, new diagnosis diabetes mellitus, new atrial fibrillation, renal impairment, revascularization procedures	patients in the telmisartan group (RR, 0.99; 95% CI, 0.91 to 1.07; *P*=0.001 for noninferiority). Combination therapy was not significantly better than ramipril alone (RR, 0.99; 95% CI, 0.92 to 1.07). There were no significant differences in the rates of secondary outcomes, except for renal dysfunction, which occurred in 10.2% of patients receiving ramipril, 10.6% of patients receiving telmisartan and 13.5% of patients receiving combination therapy (*P*<0.001 vs ramipril; no *P* value reported vs telmisartan). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs 4.2%; *P*<0.001) and angioedema (0.1% vs 0.3%; *P*=0.01) and a higher rate of hypotensive symptoms (2.6% vs 1.7%; *P*<0.001); the rate of syncope was the same in the 2 groups (0.2%). As compared with the ramipril group, combination therapy had an increased risk of hypotensive symptoms (4.8% vs 1.7%; *P*<0.001), syncope (0.3% vs 0.2%; *P*=0.03) and renal dysfunction (13.5% vs 10.2%; *P*<0.001).
PEACE Trial Investigators[43] Trandolapril (target 4 mg/day) vs placebo	DB, PC, RCT Men and women ≥50 years with stable CAD and normal or slightly reduced left ventricular function (LVEF >40% with mean 58%)	N=8,290 4.8 years (median)	Primary: Combined rate of nonfatal myocardial infarction, death from cardiovascular causes, or coronary revascularization procedures Secondary: Combinations of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, unstable angina, new CHF, stroke,	Primary: No significant differences in the primary outcome measures between trandolapril and placebo were reported (21.9% vs 22.5%; HR, 0.96; 95% CI, 0.88 to 1.06; *P*=0.43). Secondary: No significant differences in secondary outcome measures between trandolapril and placebo were reported (*P*>0.05). Side effects leading to discontinuation of study medication occurred in 14.4% of patients receiving trandolapril and 6.5% of patients receiving placebo (*P*<0.001). The rates of cough (39.1% vs 27.5%; *P*<0.01) and syncope (4.8% vs 3.9%; *P*=0.04) were higher in patients receiving trandolapril vs placebo. Note: This trial was conducted in low-risk patients with stable CAD and normal or slightly reduced left ventricular function. However, the HOPE trial was conducted in patients with coronary or other vascular disease or with diabetes and another cardiovascular risk factor and the EUROPA trial

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			PVD, and cardiac arrhythmia	was conducted in patients with evidence of CHD.
Pilote et al[44] Captopril (50 mg), enalapril (10 mg), fosinopril (10 mg), lisinopril (10 mg), perindopril (4 mg), quinapril (20 mg), and ramipril (5 mg) (mean values of actual dosages)	Nonrandomized, RETRO, cohort trial (Canada) Patients ≥65 years who were hospitalized for acute myocardial infarction and filled a prescription for an ACE inhibitor within 30 days of discharge and who continued to receive the same drug for at least 1 year	N=7,512 Average of 2.3 years since discharge	Primary: 1-year mortality following an acute myocardial infarction Secondary: Readmissions due to cardiac complications	Primary: Captopril (HR, 1.56; 95% CI, 1.13 to 2.15), enalapril (HR, 1.47; 95% CI, 1.14 to 1.89), fosinopril (HR, 1.71; 95% CI, 1.29 to 2.25), lisinopril (HR, 1.28; 95% CI, 0.98 to 1.67) and quinapril (HR, 1.58; 95% CI, 1.10 to 2.82) were associated with higher mortality than was ramipril. No statistically significant difference was reported between perindopril and ramipril (HR, 0.98; 95% CI, 0.60 to 1.60; no *P* value reported). Secondary: Enalapril (HR, 1.44; 95% CI, 1.03 to 2.01) and fosinopril (HR, 1.83; 95% CI, 1.27 to 2.62) were associated with higher readmission rates for CHF than ramipril (no *P* values reported). Readmissions for unstable angina and recurrent myocardial infarction were similar across all prescription groups.
Nissen et al[45] CAMELOT Amlodipine tablet (5 mg/day) and placebo enalapril capsule vs placebo amlodipine tablet and enalapril (10 mg/day) capsule vs placebo amlodipine	DB, MC, PC, RCT Men and women aged 30 to 79 years requiring coronary angiography for evaluation for chest pain or PCI and a diastolic pressure <100 mm Hg, with or without treatment Patients with left	N=1,991 2 years	Primary: Incidence of adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or nonfatal stroke or	Primary: Adverse cardiovascular events occurred in 23.1% of placebo-treated patients, 16.6% amlodipine-treated patients (HR, 0.69; 95% CI, 0.54 to 0.88; *P*=0.003) and 20.2% enalapril-treated patients (HR, 0.85; 95% CI, 0.67 to 1.07; *P*=0.16). The most frequent component of the primary end point, coronary revascularization, was reduced in the amlodipine group from 15.7% to 11.8% (HR, 0.73; 95% CI, 0.54 to 0.98; *P*=0.03). Hospitalization for angina was reduced in the amlodipine group from 12.8% to 7.7% (HR, 0.58; 95% CI, 0.41 to 0.82; *P*=0.002). Individual components of the primary end point generally showed fewer events with enalapril treatment vs placebo, but none of the comparisons reached statistical significance. The primary end point comparison for enalapril vs amlodipine was not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tablet and placebo enalapril capsule Doses were doubled (amlodipine 10 mg/day and enalapril 20 mg/day) after 2 weeks if the initial dose was tolerated. Participants were instructed to take only 1 tablet and 1 capsule of study medication each day if they experienced any intolerable adverse effect thought to be related to the study drug while at full dose.	main coronary artery obstruction >50%, LVEF <40% or moderate-to-severe CHF were excluded.		TIA, and any new diagnosis of PVD), nominal change in percent atheroma volume (substudy) Secondary: Incidence of adverse events; all-cause mortality, incidence of revascularization in vessels that had undergone previous stent placement	significant (HR, 0.81; 95% CI, 0.63 to 1.04; *P*=0.10). For components of the primary end point, only the rate of hospitalization for angina showed a statistically significant difference between amlodipine and enalapril (HR, 0.59; 95% CI, 0.42 to 0.84; *P*=0.003). A trend toward fewer episodes of revascularization in patients undergoing intervention at baseline was observed for amlodipine vs enalapril (HR, 0.66; 95% CI, 0.40 to 1.06; *P*=0.09). The mean change in percent atheroma volume was 0.5% for amlodipine (*P*=0.12 vs placebo), 0.8% for enalapril (*P*=0.32 vs placebo) and 1.3% for placebo. In patients with systolic blood pressure greater than the mean, the amlodipine group showed a significantly slower progression (0.2%) compared with placebo (2.3%; *P*=0.02). Compared with baseline, intravascular ultrasound showed progression in patients receiving placebo (*P*<0.001), a trend toward progression with enalapril (*P*=0.08) and no progression in patients receiving amlodipine (*P*=0.31). For the amlodipine group, correlation between blood pressure reduction and progression was *r*=0.19 (*P*=0.07). Secondary: Discontinuation from the study for treatment-emergent adverse events was low, averaging 0.4% and not statistically significant between the 3 treatment groups (*P* value not reported). The only statistically significant difference in secondary end points was that amlodipine demonstrated a significant reduction in revascularization after previous stent placement compared with placebo (4.1% vs 7.9%; HR, 0.49; 95% CI, 0.31 to 0.78; *P*=0.002). The rate of revascularization was lower than enalapril (6.2%) but not statistically significant (HR 0.66, 95% CI, 0.40 to 1.06; *P*=0.09).
Dalhof et al[46] ASCOT-BPLA Amlodipine 5 mg/day to 10 mg/day adding	MC, OL, PRO, RCT Patients 40-79 years old with hypertension and	N=19,257 5.5 years	Primary: Nonfatal myocardial infarction (including silent myocardial infarction) and fatal CHD	Primary: No statistically significant difference in nonfatal myocardial infarction and fatal CHD was reported between the amlodipine plus perindopril group compared to the atenolol plus bendroflumethiazide groups (HR, 0.90; 95% CI, 0.79 to 1.02; *P*=0.1052).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
perindopril 4 mg/day to 8 mg/day as needed vs atenolol 50 mg/day to 100 mg/day adding bendroflumethiazide 1.25 mg/day to 2.5 mg/day and potassium as needed If blood pressure was still not achieved, a third drug, an α-blocker (doxazosin 4 mg/day to 8 mg/day), was added to the regimen.	at least 3 other cardiovascular risk factors (left ventricular hypertrophy, other specified abnormalities on ECG, type 2 diabetes, PAD, history of stroke or TIA, male, age ≥55 years, microalbuminuria or proteinuria, smoking, total cholesterol to HDL-C ratio ≥6, or family history of CHD)		Secondary: All-cause mortality, total stroke, primary end points minus silent myocardial infarction, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, nonfatal and fatal heart failure, effects on primary end point and on total cardiovascular events and procedures among prespecified subgroups Tertiary: Silent myocardial infarction, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias, development of diabetes, development of renal impairment	Secondary: Significantly greater reductions in the following secondary end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: all- cause mortality (*P*=0.0247), total stroke (*P*=0.0003), primary end points minus silent myocardial infarction (*P*=0.0458), all coronary events (*P*=0.0070), total cardiovascular events and procedures (*P*<0.0001), and cardiovascular mortality (*P*=0.0010). There were no significant differences in nonfatal and fatal heart failure between the two treatment groups (*P*=0.1257). The study was terminated early due to higher mortality and worse outcomes on several secondary end points observed in the atenolol study group. Tertiary: Significantly greater reductions in the following end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: unstable angina (*P*=0.0115), PAD (*P*=0.0001), development of diabetes (*P*<0.0001), and development of renal impairment (*P*=0.0187). There were no significant differences in the incidence of silent myocardial infarction (*P*=0.3089), chronic stable angina (*P*=0.8323) or life-threatening arrhythmias (*P*=0.8009) between the two treatment groups. There was no significant difference in the percent of patients who stopped therapy because of an adverse event between the 2 treatment groups (overall 25%; no *P* values reported). There was, however, a significant difference in favor of amlodipine plus perindopril in the proportion of patients who stopped trial therapy because of a serious adverse events (2% vs 3%; *P*<0.0001).
Heart Failure (ACE Inhibitor vs Placebo or Another ACE Inhibitor)				
Pfeffer, Braunwald et al[47]	DB, MC, PC, RCT	N=2,231	Primary: Mortality from all	Primary: Mortality from all causes was significantly reduced in the captopril group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
SAVE Captopril up to 50 mg TID vs placebo	Patients ≥21 and <80 years of age who had an acute myocardial infarction within 3-16 days and left ventricular dysfunction with an ejection fraction ≤40% but without overt heart failure or symptoms of myocardial ischemia	42 months (average)	causes, mortality from cardiovascular causes, mortality combined with a decrease in ejection fraction of at least 9 units in surviving patients, cardiovascular morbidity (severe CHF or recurrence of a fatal or nonfatal myocardial infarction), combination of cardiovascular mortality and morbidity Secondary: Not reported	(20%) vs placebo group (25%) for a 19% reduction in the risk of mortality from all causes (95% CI, 3% to 25%; *P*=0.019). The incidence of fatal cardiovascular events was consistently reduced in the captopril group with a 21% reduced risk of mortality from cardiovascular causes (*P*=0.014). The incidence of nonfatal major cardiovascular events was consistently reduced in the captopril group with a 25% reduced risk of recurrent myocardial infarction (*P*=0.015), 37% reduced risk for the development of severe heart failure (*P*<0.001), and 22% reduced risk of CHF requiring hospitalization (*P*=0.019). Secondary: Not reported Long-term captopril administration was associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events.
CONSENSUS Trial Study Group[48] Enalapril 2.5 to 40 mg per day vs placebo	DB, MC, PC, PG, RCT Patients with severe CHF (NYHA class IV symptoms), patients with recent myocardial infarction and unstable angina were excluded	N=253 188 days (average)	Primary: 6-month mortality and the cause of death Secondary: 12-month mortality and overall mortality	Primary: Mortality at 6 months was 26% and 44% for patients in the enalapril and placebo groups, respectively, for an overall reduction of 40% for enalapril (*P*=0.002). Secondary: At 12 months, enalapril reduced mortality by 31% compared to placebo (*P*=0.001). By the end of the study, there had been 50 deaths in the enalapril group and 68 deaths in the placebo group for a reduction of 27% (*P*=0.003). The entire reduction in total mortality was found to be among patients with progressive heart failure (a reduction of 50%), whereas no difference was seen in the incidence of sudden cardiac death. Note: The study was stopped early due to clear benefit with enalapril. On the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				date of termination, 253 of the planned 400 patients were enrolled.
SOLVD Investigators[49] SOLVD Treatment Trial Enalapril 2.5 to 20 mg per day vs placebo	DB, MC, PC, RCT Patients with CHF (90% were in NYHA class II and III) and LVEF ≤35% receiving conventional therapy	N=2,569 41.4 months (average)	Primary: Mortality, rate of hospitalization for heart failure Secondary: Not reported	Primary: Death was reported in 35.2% and 39.7% of patients receiving enalapril and placebo, respectively (risk reduction, 16%; 95% CI, 5% to 26%; *P*=0.0036). Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive heart failure (risk reduction, 22%; 95% CI, 6% to 35%; no *P* value reported). There was little apparent effect of treatment on deaths classified as due to arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening heart failure (risk reduction, 26%; 95% CI, 18% to 34%; *P*<0.0001). Secondary: Not reported
SOLVD Investigators[50] SOLVD Prevention Trial Enalapril 2.5 mg to 20 mg per day vs placebo	DB, MC, PC, RCT Patients between the ages of 21 to 80 years with heart disease and an ejection fraction of ≤35% who were not receiving diuretics, digoxin or vasodilators for the treatment of heart failure	N=4,228 37.4 months (average)	Primary: All-cause mortality, incidence of heart failure, rate of hospitalization for heart failure Secondary: Not reported	Primary: Enalapril resulted in an 8% reduction in risk for all-cause mortality (*P*=0.30). The difference was entirely due to a reduction in deaths due to cardiovascular causes, primarily progressive heart failure (risk reduction, 12%; *P*=0.12). In the placebo group, 30.2% of patients developed heart failure compared to 20.7% for enalapril (risk reduction, 37%; *P*<0.001). Rates of first hospitalization and multiple hospitalizations for CHF were higher with placebo (12.9% and 4.8%) than enalapril (8.7% and 2.7%; both *P*<0.001). The total number of deaths and cases of heart failure were lower in the enalapril group than in the placebo group (risk reduction, 29%; *P*<0.001). In addition, fewer patients given enalapril died or were hospitalized for heart failure (risk reduction, 20%; *P*<0.001). Secondary: Not reported
Tu et al[51]	RETRO,	N=6,753	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Comparison between enalapril (comparator drug) and lisinopril, ramipril and other ACE inhibitors (benazepril, captopril, cilazapril*, fosinopril, perindopril, quinapril and trandolapril)	cohort study Patients >65 years with newly diagnosed CHF initiated on ACE inhibitors who survived ≥30 days after hospital discharge	≤2 years	Combined end point of readmission for CHF as a primary diagnosis or mortality Secondary: CHF readmission alone and mortality alone	Relative to enalapril users, there were no significant differences in combined end point of readmission for CHF or mortality with lisinopril (AHR, 1.08; 95% CI, 0.94 to 1.23), ramipril (AHR, 1.06; 95% CI, 0.92 to 1.24) or other ACE inhibitors (AHR, 1.02; 95% CI, 0.90 to 1.17). Secondary: There were no significant differences among groups in readmission for CHF: enalapril 13% (AHR 1), lisinopril 15% (AHR, 1.11; 95% CI, 0.92 to 1.32), ramipril 15% (AHR, 1.19; 95% CI, 0.99 to 1.45), and other ACE inhibitors 15% (AHR, 1.13; 95% CI, 0.96 to 1.34). There were no significant differences among groups in mortality: enalapril 12% (AHR 1), lisinopril 13% (AHR, 1.09; 95% CI, 0.90 to 1.31), ramipril 12% (AHR, 0.97; 95% CI, 0.78 to 1.20), and other ACE inhibitors 11% (AHR, 0.94; 95% CI, 0.78 to 1.13).
Packer et al[52] ATLAS Lisinopril low dose (target 2.5 to 5 mg/day) vs lisinopril high dose (target 32.5 to 35 mg/day)	DB, RCT Patients with NYHA class II, III, or IV symptoms of heart failure associated with a LVEF ≤30% despite treatment with diuretics for ≥2 months	N=3,164 39-58 months	Primary: All-cause mortality Secondary: cardiovascular mortality, hospitalizations (for any reason and for cardiovascular reasons), combinations of the primary and secondary end points	Primary: High-dose lisinopril was associated with a nonsignificant 8% lower risk of all-cause mortality compared to low-dose lisinopril (*P*=0.128). Secondary: Cardiovascular mortality was reported in 40.2% and 37.2% of patients receiving low-dose and high-dose lisinopril, respectively (*P*=0.073). High-dose lisinopril resulted in a 12% lower risk of death or hospitalizations for any reason (*P*=0.002), a 9% lower risk of cardiovascular mortality and hospitalization for cardiovascular reason (*P*=0.027) and 24% fewer hospitalizations for heart failure (*P*=0.002). Dizziness and renal insufficiency were observed more frequently in the high-dose group, but the 2 groups were similar in the number of patients requiring discontinuation of the study medication.
AIRE Study Investigators[53] Ramipril 2.5 to 5 mg BID	DB, MC, PC, RCT Men and women at least 18 years old with acute	N=2,006 15 months (average)	Primary: All-cause mortality Secondary: First event in an individual patient	Primary: On the intention-to-treat analysis, all-cause mortality was significantly lower for patients randomized to receive ramipril (17%) than placebo (23%). The observed risk reduction was 27% (95% CI, 11% to 40%; *P*=0.002). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Treatment was begun on day 3 to day 10 after acute myocardial infarction.	myocardial infarction and clinical evidence of heart failure, patients with severe heart failure (eg, NYHA grade IV) were excluded		(death, progression to severe/resistant heart failure, re-infarction, or stroke)	Analysis of prespecified secondary outcomes revealed a 19% risk reduction in the ramipril group compared to placebo (95% CI, 5% to 31%; *P*=0.008).
Kober et al[54] TRACE Trandolapril 1 to 4 mg QD vs placebo Medication was started between day 3 and 7 after the myocardial infarction.	DB, MC, PC, RCT Men and women >18 years who were hospitalized with a recent myocardial infarction and an LVEF ≤35%	N=1,749 24-50 months	Primary: Death from any cause Secondary: Death from a cardiovascular cause, sudden death, progression to severe heart failure (defined as the first of the following events: hospital admission for heart failure, death due to progressive heart failure, or heart failure necessitating the administration of open-label ACE inhibition), recurrent infarction, change in the wall-motion index	Primary: During the study, 34.7% of patients in the trandolapril group died compared with 42.3% in the placebo group (*P*=0.001). The relative risk of death in the trandolapril group was 0.78 compared to placebo (95% CI, 0.67 to 0.91). Secondary: Trandolapril reduced the risk of death from cardiovascular causes (RR, 0.75; 95% CI, 0.63 to 0.89; *P*=0.001) and sudden death (RR, 0.76; 95% CI, 0.59 to 0.98; *P*=0.03). Progression to severe heart failure was less frequent in the trandolapril group (RR, 0.71; 95% CI, 0.56 to 0.89; *P*=0.003). The risk of recurrent fatal or nonfatal myocardial infarction was not significantly reduced (RR, 0.86; 95% CI, 0.66 to 1.13; *P*=0.29). After three months, the mean change from the base-line index was 0.09 in the trandolapril group and 0.06 in the placebo group (*P*=0.03) but this statistically significant difference was absent at 6 and 12 months.
Heart Failure (ACE Inhibitor vs Agents From Other Therapeutic Classes)				
Pitt, Segal et al[55] ELITE	DB, MC, PG, RCT	N=722 1 year	Primary: Change in renal function	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Captopril 50 mg TID vs losartan 50 mg QD	Patients ≥65 years with symptomatic heart failure (NYHA class II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy		Secondary: Composite of death and/or hospital admission for heart failure, all-cause mortality, admission for heart failure, NYHA class, admission for myocardial infarction or unstable angina	Secondary: Death and/or hospital admission for heart failure was recorded in 9.4% of patients receiving losartan and 13.2% for patients receiving captopril (risk reduction, 32%; 95% CI, –4% to +55%; *P*=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8% vs 8.7%; risk reduction, 46%; 95% CI, 5% to 69%; *P*=0.035). Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline. Admission to hospital for any reason was less frequent with losartan than with captopril treatment (22.2% vs 29.7%; *P*=0.014). More patients discontinued therapy due to adverse events with captopril (20.8%) than losartan (12.2%; *P*=0.002).
Pitt, Poole-Wilson et al[56] ELITE II Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥60 years old with symptomatic heart failure (NYHA II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=3,152 555 days (mean follow-up)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between losartan (17.7%) and captopril (15.9%; HR, 1.13; 95% CI, 0.95 to 1.35; *P*=0.16). Secondary: Sudden death or resuscitated cardiac arrest was observed in 9.0% of patients receiving losartan and 7.3% of patients receiving captopril (HR, 1.25; 95% CI; 0.98 to 1.60; *P*=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse events (9.7% vs 14.7%; *P*<0.001), including cough (0.3% vs 2.7%). Note: ELITE II trial was a larger follow-up trial to the ELITE I trial to confirm the secondary end point from the ELITE I trial which reported a greater reduction in all-cause mortality with losartan compared with captopril.
Dickstein et al[57] OPTIMAAL	DB, MC, PG, RCT Patients ≥50 years	N=5,477 2.7 years (mean)	Primary: All-cause mortality Secondary:	Primary: No significant difference in all-cause mortality was reported between patients receiving losartan and captopril (18% vs 16%, respectively; RR, 1.13; 95% CI, 0.99 to 1.28; *P*=0.07).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Captopril 50 mg TID vs losartan 50 mg QD	(mean age 67.4 years) with an acute myocardial infarction and signs or symptoms of heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction		Composite of sudden cardiac death or resuscitated cardiac arrest	Secondary: No significant difference in sudden cardiac death or resuscitated cardiac arrest was reported between patients receiving losartan and captopril (9% vs 7%; RR, 1.19; 95% CI, 0.98 to 1.43; *P*=0.07). Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (17% vs 23%; *P*<0.0001).
Pfeffer, McMurray et al[58] VALIANT Captopril 50 mg TID vs valsartan 160 mg BID vs combination valsartan 80 mg BID and captopril 50 mg TID	DB, MC, RCT Men and women ≥18 years with an acute myocardial infarction that was complicated by clinical or radiologic signs of heart failure and/or evidence of left ventricular systolic dysfunction	N=14,703 24.7 months	Primary: All-cause mortality Secondary: Death from cardiovascular causes, recurrent myocardial infarction, hospitalization for heart failure	Primary: No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (*P*=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (*P*=0.73). Secondary: The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (*P*=0.20). The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (*P*=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash, and taste disturbance were more common in the captopril group.
McKelvie et al[59] RESOLVD Pilot Study	DB, PG, MC, RCT Patients with	N=768 43 weeks	Primary: Change in 6-minute walk distance	Primary: There were no significant differences among the groups with regards to the 6-minute walk distance over the 43-week study period (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Enalapril 10 mg BID vs candesartan 4 to 16 mg QD vs combination candesartan 4 to 8 mg QD and enalapril 10 mg BID	CHF (NYHA classes II to IV), a 6 minute walk distance of 500 meters or less, and an ejection fraction <40%		Secondary: Change in NYHA functional class, quality of life, ejection fraction, ventricular volumes, neurohormone levels, safety	Secondary: There were no significant differences among the groups with regards to the NYHA functional class or quality of life at 18 or 43 weeks (*P* values not reported). Ejection fraction increased more with candesartan plus enalapril than monotherapy with either agent; however, the difference was not statistically significant (*P*=NS). End-diastolic volumes (*P*<0.01) and end-systolic volumes (*P*<0.05) increased less with combination therapy than with monotherapy with either agent. Aldosterone decreased with combination therapy at 17 but not 43 weeks compared with candesartan or enalapril (*P*<0.05). Brain natriuretic peptide decreased with combination therapy compared with candesartan and enalapril alone (*P*<0.01). Blood pressure decreased with combination therapy compared with candesartan or enalapril alone (*P*<0.05). Compared with enalapril, potassium decreased with candesartan use (*P*<0.05) and increased with candesartan plus enalapril (*P*<0.05). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups. There were no significant differences in creatinine, mortality, or hospitalizations for CHF or any cause among the 3 groups.
Cohn et al[60] V-HEFT II Enalapril 20 mg daily vs hydralazine 300 mg plus isosorbide dinitrate 160 mg daily	AC, DB, MC, RCT Men between the ages of 18 and 75 years with chronic heart failure receiving digoxin and diuretic therapy	N=804 2 years	Primary: Mortality Secondary: Peak oxygen consumption during exercise, LVEF	Primary: Mortality after 2 years was significantly lower in the group treated with enalapril (18%) than hydralazine plus isosorbide dinitrate (25%; *P*=0.016), and overall mortality tended to be lower (*P*=0.08). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (NYHA class I or II). Secondary: Peak oxygen consumption during exercise was increased only by

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				hydralazine plus isosorbide dinitrate (*P*<0.05). While LVEF increased with both regimens during the 2 years after randomization, LVEF increased more (*P*<0.05) during the first 13 weeks in the hydralazine plus isosorbide dinitrate group.
Hypertension				
ALLHAT[61] Lisinopril 10 to 40 mg/day vs amlodipine 2.5 to 10 mg/day vs chlorthalidone 12.5 to 25 mg/day Doses were titrated to achieve a goal blood pressure of <140/90 mm Hg.	DB, MC, RCT Patients ≥55 years with hypertension and at least 1 additional CHD risk factor	N=33,357 4.9 years (mean follow-up)	Primary: Combined fatal CHD or nonfatal myocardial infarction Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD (primary outcome, coronary revascularization and hospitalized angina), combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization, heart failure, and PAD)	Primary: There were no significant differences in the primary outcome between lisinopril (11.4%), amlodipine (11.3%) and chlorthalidone (11.5%). Secondary: All-cause mortality did not differ between groups. Five-year SBPs were significantly higher in the lisinopril (2 mm Hg; *P*<0.001) and amlodipine groups (0.8 mm Hg; *P*=0.03) compared to chlorthalidone, and 5-year DBPs were significantly lower with amlodipine (0.8 mm Hg; *P*<0.001). Amlodipine had a higher 6-year rate of heart failure compared to chlorthalidone (10.2% vs 7.7%; RR, 1.38; 95% CI, 1.25 to 1.52; no *P* value reported). Lisinopril had a higher 6-year rate of combined cardiovascular disease (33.3% vs 30.9%; RR, 1.10; 95% CI, 1.05 to 1.16); stroke (6.3% vs 5.6%; RR, 1.15; 95% CI, 1.02 to 1.30) and heart failure (8.7% vs 7.7%; RR, 1.19; 95% CI, 1.07 to 1.31) (no *P* values reported).
Estacio et al[62] ABCD Enalapril 5 to 40 mg/day vs	DB, PRO, RCT Patients between the ages of 40 and 74 years with NIDDM, baseline DBP ≥90 mm Hg and receiving no	N=470 67 months	Primary: Effect of intensive (target DBP of 75 mm Hg) or moderate (target DBP between 80-89 mm Hg) blood-pressure control on	Primary: Analysis of the 470 patients in the trial who had hypertension (DBP ≥90 mm Hg) showed similar control of blood pressure, blood glucose and lipid concentrations between the 2 study medications throughout the 5 years of follow-up. Secondary: Nisoldipine was associated with a higher incidence of fatal and nonfatal

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nisoldipine 10 to 60 mg/day	antihypertensive medications at the time of randomization		the incidence and progression of complications of diabetes; compare enalapril to nisoldipine as a first-line antihypertensive agent Secondary: Incidence of myocardial infarction	myocardial infarction than enalapril (RR, 7.0; 95% CI, 2.3 to 21.4; no *P* value reported).
Wing et al[63] ANBP Enalapril and HCTZ were recommended as initial therapy; however, the choice of the specific agent and dose was made by the family practitioner.	MC, OL, PRO, RCT Patients 65 to 84 years of age with average SBP while sitting of at least 160 mm Hg or an average DBP of at least 90 mm Hg (if the systolic blood pressure was at least 140 mm Hg)	N=6,083 4.1 years (median)	Primary: All cardiovascular events or death from any cause (both initial and subsequent fatal and nonfatal cardiovascular events) Secondary: Not reported	Primary: By the end of the study, blood pressure had decreased to a similar extent in both groups (a decrease of 26/12 mm Hg). There were 695 cardiovascular events or deaths from any cause in the ACE inhibitor group (56.1 per 1,000 patient-years; HR, 0.89; 95% CI, 0.79 to 1.00; *P*=0.05) compared to 736 in the diuretic group (59.8 per 1,000 patient-years). The beneficial effects of ACE inhibitor treatment were more evident in male subjects (HR, 0.83; 95% CI, 0.71 to 0.97; *P*=0.02). The rates of nonfatal cardiovascular events and myocardial infarction decreased with ACE inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE inhibitor group). Secondary: Not reported
Whelton et al[64] Lisinopril 10 to 40 mg QD	DB, MC, PG, RCT Patients with	N=70 Up to 8 weeks	Primary: Reduction in blood pressure in both ambulatory and	Primary: Lisinopril-treated patients showed significantly greater reductions in SBP and DBP measured by 24-hour ambulatory blood pressure monitoring compared with captopril-treated patients (*P*=0.023 and *P*=0.007,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs captopril 25 to 100 mg BID Doses were titrated until patients responded to treatment (defined by a decrease in office diastolic pressure to <90 mm Hg or at least a 10 mm Hg decrease from baseline).	mild-to-moderate essential hypertension		office settings Secondary: Not reported	respectively). Greater reductions (*P*<0.05) were also noted in patients receiving lisinopril at hours 10 to 12, suggesting 2 blood pressure troughs for those receiving captopril. The difference in mean reductions between treatment groups from baseline to the final visit approached statistical significance for office SBP (*P*=0.06) and DBP (*P*=0.09) in favor of patients receiving lisinopril. Both drugs were well tolerated, and no patients withdrew form either treatment group. Secondary: Not reported
Beckett et al[65] HYVET Indapamide 1.5 mg/day vs placebo Perindopril 2 to 4 mg/day or matching placebo was added if necessary to achieve the target blood pressure of 150/80 mm Hg.	DB, MC, PC, RCT Patients ≥80 years (mean age 84 years) with sustained SBP ≥160 mm Hg	N=3,845 1.8 years (mean follow-up)	Primary: Fatal or nonfatal stroke Secondary: Death from any cause, death from cardiovascular causes, death from stroke	Primary: At 2 years, 73.4% of patients in the active-treatment groups were receiving indapamide plus perindopril. Mean blood pressure while sitting was 15.0/6.1 mm Hg lower with active-treatment than placebo (no *P* values reported). Active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% CI, –1 to 51; *P*=0.06). Secondary: Active treatment was associated with a 21% reduction in the rate of death from any cause (95% CI, 4 to 35; *P*=0.02), a 23% reduction in the rate of death from cardiovascular causes (95% CI, –1 to 40; *P*=0.06) and a 39% reduction in the rate of death from stroke (95% CI, 1 to 62; *P*=0.05). Active treatment was associated with a 64% reduction in the rate of heart failure (95% CI, 42 to 78; *P*<0.001). Fewer serious adverse events were reported in the active-treatment group (358 vs 448; *P*=0.001).
Tytus et al[66] Trandolapril 1 to 4 mg/day	MC, OL, PRO Patients (mean age 56.6 years)	N=1,683 26 weeks	Primary: Percentage of patients reaching target blood	Primary: At 14 weeks of treatment, 71.2% of patients who were treated with trandolapril monotherapy reached SBP/DBP <140/90 mm Hg.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
At 14 weeks after treatment initiation, subjects not achieving blood pressure targets could receive a combination of trandolapril 4 mg/day plus verapamil 240 mg/day with or without a diuretic.	with stage 1 or 2 hypertension who were treatment naïve (82%) or uncontrolled on a diuretic (11%) or calcium-channel blocker (7%); uncontrolled hypertension was defined as ≥140/90 mm Hg in subjects with no other risk factors or ≥130/80 mm Hg in subjects with diabetes or kidney disease		pressure at 14 weeks Secondary: Percentages of subjects with stage 1 and 2 hypertension who achieved target blood pressure, percentages of subjects who achieved a drop in SBP of ≥20 mm Hg and/or DBP ≥10 mm Hg, absolute changes in SBP and DBP, adverse events	Secondary: At 26 weeks, 73.4% of patients achieved a target level of SBP/DBP <140/90 mm Hg. Of the 683 subjects with stage 2 hypertension, 64.6% achieved the target level after 14 weeks of trandolapril and 67.9% after 26 weeks. At 14 weeks, 78.8% of subjects treated with a trandolapril regimen experienced a decrease in SBP of ≥20 mm Hg or a decrease in DBP of ≥10 mm Hg. Statistically significant (*P*<0.001) and clinically relevant mean decreases in SBP of –16.1 mm Hg and in DBP of –8.8 mm Hg were observed from 4 weeks of treatment onward for the overall study population. The mean reductions in SBP and DBP were –21.5 and –11.9 mm Hg, respectively at 14 weeks (*P*<0.001), and –22.4 and –12.7 mm Hg, respectively, at 26 weeks (*P*<0.001). A total of 343 predominantly mild, nonserious adverse events were attributed to the study drugs, reported by 15.3% of the 1,650 subjects. The most frequently reported nonserious adverse events were cough (6.3%); gastrointestinal disorders (2.3%), predominantly nausea; and headache (2.1%). No serious adverse events were attributed to the study treatment.
Pauly et al[67] Trandolapril 4 mg QD vs captopril 50 mg BID If blood pressure was not normalized at 8 weeks, HCTZ 25 mg was added.	DB, MC, RCT Patients between 21 to 65 years with mild-to-moderate essential hypertension (DBP of 95-115 mm Hg)	N=180 16 weeks	Primary: Morning pre-dosing supine DBP at 8 weeks of monotherapy Secondary: Supine SBP at 8 weeks of monotherapy, blood pressure at 16 weeks of therapy (including 8 weeks of monotherapy and 8 weeks of combination therapy	Primary: Significantly greater mean reductions in supine DBP in the trandolapril group vs captopril group were observed after 8 weeks of monotherapy (–13.5 vs –10.1 mm Hg; *P*=0.007). Secondary: Differences in supine SBP between treatment groups approached significance after 8 weeks of monotherapy (*P*=0.06). Both SBP and DBP were significantly reduced at all time points compared with baseline for both treatment groups at the end of the study (*P*<0.05). The proportion of patients whose blood pressure normalized (supine and standing blood pressure ≤160/90 mm Hg) at the end of the study was 61% for trandolapril and 44% for captopril (*P*=0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			with HCTZ)	The overall proportion of responders (DBP fell by ≥10 or to <90 mm Hg) was significantly greater in the trandolapril group (77%) than in the captopril group (58%; *P*<0.007).
Vaur et al[68] Trandolapril 2 mg QAM vs enalapril 20 mg Q AM	DB, RCT Patients between 18 to 70 years with mild-to-moderate primary hypertension	N=88 3 weeks	Primary: 24-hour ambulatory SBP and DBP over an active 24-hour period and subsequent 24-hour period (to mimic a missed dose) Secondary: Not reported	Primary: Both trandolapril and enalapril showed similar reductions in SBP and DBP over the 24-hour period. In the trandolapril group, SBP and DBP decreased from 148/92 to 135/83 mm Hg (*P*<0.001). In the enalapril group, SBP and DBP decreased from 143/91 to 133/83 mm Hg (*P*<0.001). The trough/peak ratio on active treatment was 90% (SBP) and 54% (DBP) in the trandolapril group and 49% (SBP and DBP) in the enalapril group. Following the missed dose, trough/peak ratio decreased to 58% (SBP)/36% (DBP) for trandolapril and 10% (SBP)/19% (DBP) for enalapril. The blood pressure control was better sustained with trandolapril, such that significant falls in blood pressure were observed during the daytime, nighttime and early morning periods after a missed dose, whereas during the same periods, enalapril only significantly reduced blood pressure in the daytime period. Secondary: Not reported
Blood Pressure Lowering Treatment Trialists' Collaboration[69] ACE inhibitors (17 trials) vs ARBs (9 trials)	MA of RCT published by the end of 2004 Patients with high blood pressure, diabetes, history or CHD or cerebrovascular disease	26 large-scale trials, N=146,838	Primary: Nonfatal myocardial infarction or death from CHD, including sudden death; heart failure causing death or requiring hospitalization; nonfatal stroke or death from cerebrovascular disease Secondary: Not reported	Primary: From a total of 146,838 individuals with high blood pressure or an elevated risk of cardiovascular disease, major cardiovascular events were documented in 22,666 patients during follow-up. The analyses showed comparable blood pressure-dependent reductions in risk with ACE inhibitors and ARBs (*P*≥0.3 for all 3 outcomes). ACE inhibitors produced a blood pressure-independent reduction in the relative risk of CHD of approximately 9% (95% CI, 3 to 14%). No similar effect was detected for ARBs, and there was some evidence of a difference between ACE inhibitors and ARBs in this regard (*P*=0.002). For both stroke and heart failure, there was no evidence of any blood pressure-independent effects of either ACE inhibitors or ARBs. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The authors concluded that there are similar blood pressure-dependent effects of ACE inhibitors and ARBs for the risks of stroke, CHD and heart failure. They also stated that for ACE inhibitors but not ARBs there is evidence of blood pressure-independent effects on the risk of major coronary disease events.
Diabetes/Diabetic Nephropathy/Renal Dysfunction				
Hou et al[70] ROAD Benazepril 10 mg/day vs individual uptitration (10 to 40 mg/day with median dose of 20 mg/day) or losartan 50 mg/day vs individual uptitration (50 to 200 mg/day with median dose of 100 mg/day) Uptitration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained.	OL, PRO, RCT Patients aged 18-70 years with proteinuria and chronic renal insufficiency who did not have diabetes	N=360 3.7 years (median follow-up)	Primary: Time to composite of doubling of serum creatinine, ESRD or death Secondary: Changes in level of proteinuria, rate of progression of renal disease	Primary: Compared with the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through uptitration were associated with a 51% and 53% reduction in the risk for the primary end point (*P*=0.028 and *P*=0.022, respectively). There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages (no *P* values reported). Secondary: Optimal antiproteinuric dosages of benazepril and losartan at comparable blood pressure control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared with their conventional dosages. There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages (no *P* values reported). Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (*P*>0.05). There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in any of the treatment arms (no *P* values reported).
Barnett et al[71] DETAIL Enalapril 20 mg/day	DB, MC, PG, RCT Patients aged 35 to 80 years with	N=250 5 years	Primary: Change in the GFR Secondary: Annual changes in	Primary: After 5 years, GFR decreased by 17.9 mL/minute/1.73 m^2 with telmisartan compared to 14.9 mL/min/1.73 m^2 with enalapril (mean difference, –3.0 mL/min/1.73 m^2; 95% CI, –7.6 to 1.6). Therefore, the changes in GFR were comparable between the groups (*P* value not specified).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs telmisartan 80 mg/day	type 2 diabetes and hypertension		GFR, serum creatinine level, urinary albumin excretion, and blood pressure; rates of ESRD and cardiovascular events; all-cause mortality	Secondary: The effects of the 2 agents on the secondary end points were not significantly different after 5 years.
Mogensen et al[72] CALM Lisinopril 20 mg QD vs candesartan 16 mg QD vs lisinopril 20 mg QD plus candesartan 16 mg QD Patients received 12 weeks monotherapy followed by an additional 12 weeks of monotherapy or combination therapy.	DB, DD, MC, PG, RCT Patients 30 to 75 years old with hypertension, type 2 diabetes, and micro-albuminuria	N=199 24 weeks	Primary: Blood pressure and urinary albumin:creatinine ratio Secondary: Not reported	Primary: At 12 weeks, mean reductions in DBP were 9.7 mm Hg (P<0.001) and 9.5 mm Hg (P<0.001), respectively, and in urinary albumin:creatinine ratio were 46% (P<0.001) and 30% (P<0.001) for lisinopril and candesartan, respectively. Compared to either agent alone, at 24 weeks the combination of lisinopril plus candesartan resulted in 16.3 mm Hg reduction in mean DBP vs 10.4 mm Hg for candesartan alone (P<0.001) and 10.7 mm Hg for lisinopril alone (P<0.001). The reduction in urinary albumin:creatinine ratio with combination treatment (50%) was greater than with lisinopril alone (39%; P<0.001) and candesartan alone (24%; P=0.05). All treatments were generally well tolerated. Secondary: Not reported
DREAM Trial Investigators[73] Ramipril up to 15 mg/day	DB, MC, PC, PRO, RCT, 2-by-2 factorial design Adults aged 30 years or more	N=5,269 3 years (median)	Primary: Composite of newly diagnosed diabetes or death Secondary:	Primary: The composite primary outcome did not differ significantly between the ramipril group (18.1%; HR, 0.91; 95% CI, 0.81 to 1.03; P=0.15) and the placebo group (19.5%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Patients were concurrently randomly assigned to receive either rosiglitazone or matching placebo with a 2×2 factorial design. Only the results relevant to ramipril are presented in this review.	with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease		Regression to normoglycemia, glucose levels, composite of cardiac and renal events (were not yet analyzed at the time of this publication)	Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (HR, 1.16; 95% CI, 1.07 to 1.27; *P*=0.001). At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group than in the placebo group (*P*=0.07), though plasma glucose levels 2 hours after an oral glucose load were significantly lower in the ramipril group (*P*=0.01).
GISEN Group[74] REIN Ramipril 1.25 mg/day vs placebo	DB, PC, RCT Patients between 18 and 70 years who were either normotensive (<140/90 mm Hg) or hypertensive with chronic nephropathy and persistent proteinuria, who had not received ACE inhibition therapy for at least 2 months	N=166 (stratum 2) 16 months	Primary: Rate of GFR decline, extent to which this effect was dependent on the drug's antiproteinuric effect Secondary: Blood pressure control, time to doubling of baseline serum creatinine or progression to end-stage renal failure, cardiovascular complications, total and cardiovascular mortality	Primary: Mean rate of GFR decline per month was significantly lower in the ramipril group than in the placebo group (0.53 mL/minute vs 0.88 mL/minute; *P*=0.03). Among the ramipril-assigned patients, percentage reduction in proteinuria was inversely correlated with decline in GFR (*P*=0.035) and predicted the reduction in risk of doubling of baseline creatinine or end-stage renal failure (18 ramipril vs 40 placebo; *P*=0.04). Secondary: Blood pressure control and the overall number of cardiovascular events were similar in the 2 treatment groups. Fifty-eight patients (18 in the ramipril group and 40 in the placebo group) reached the combined end point of doubling of baseline serum creatinine concentration or end-stage renal failure (*P*=0.02). The risk of progression was still significantly reduced after adjustment for changes in SBP (*P*=0.04) and DBP (*P*=0.04) with ramipril, but not after adjustment for changes in proteinuria. Note: Originally, 352 patients were placed into stratum 1 (urinary protein excretion exceeding 1.0 g/24 hours) or stratum 2 (urinary protein excretion

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				exceeding 3.0 g/24 hours). At the second planned interim analysis, the difference in decline in GFR between the ramipril and placebo groups in stratum 2 was highly significant (*P*=0.001). The Independent Adjudicating Panel therefore decided to open the randomization code and do the final analysis in this stratum while stratum 1 continued in the trial.
Wright et al[75] AASK Ramipril 2.5 to 10 mg/day vs amlodipine 5 to 10 mg/day vs metoprolol 50 to 200 mg/day	DB, MC, RCT, three-by-two, factorial trial Patients were self-identified African Americans aged 18 to 70 years with hypertension and a GFR between 20 and 65 mL/minute/ 1.73 m^2 and no other identified cause of renal insufficiency	N=1,094 3-6.4 years	Primary: Rate of change in GFR (grouped by usual blood pressure [MAP goal 102 to 107 mm Hg] vs lower blood pressure [≤92 mm Hg]) Secondary: Clinical composite outcome (reduction in GFR by 50% or more, ESRD, or death)	Primary: No significant difference in primary outcome was reported between the usual blood pressure group compared with the lower blood pressure group (*P*=0.24). None of the drug group comparisons showed consistently significant differences in the GFR slope. Secondary: The lower blood pressure goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower blood pressure group, 2%; 95% CI, –22% to 21%; *P*=0.85). Ramipril resulted in significant risk reductions in the clinical composite outcomes compared with amlodipine (38%; 95% CI, 14% to 56%; *P*=0.004) and metoprolol (22%; 95% CI, 1% to 38%; *P*=0.04). There was no significant difference in the clinical composite outcome between the amlodipine and metoprolol groups.
Nakao et al[76] COOPERATE Trandolapril 3 mg/day vs losartan 100 mg/day vs trandolapril and	DB, MC, PC, RCT Patients aged 18 to 70 years with chronic nephropathy (nondiabetic renal disease)	N=263 3 years	Primary: Composite of time to doubling of serum creatinine or ESRD Secondary: Changes in blood pressure, daily urinary protein excretion, adverse effects	Primary: The combined end point was reached in 11% of patients in the combination trandolapril and losartan group compared with 23% of patients in the trandolapril (*P*=0.018) and 23% of patients in the losartan group (*P*=0.016). Secondary: Mean SBP and DBP reductions were similar among the 3 treatment groups (*P*=0.109). All patients receiving active treatment had significant decreases in urinary protein excretion, but the greatest difference was seen with the combination trandolapril and losartan group compared to trandolapril or losartan (–75.6%, –44.3% and –42.1%, respectively; *P*=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
losartan at equivalent doses				The frequency of adverse events did not differ between groups, although a slightly higher occurrence of hyperkalemia and dry cough was recorded in the trandolapril and combination groups than in the losartan group (*P* value not specified).
Ruggenenti et al[77] BENEDICT Trandolapril 2 mg/day vs verapamil SR 240 mg/day vs trandolapril 2 mg/day plus verapamil SR 180 mg/day (fixed-dose combination) vs placebo	DB, MC, RCT Patients ≥40 years with type 2 diabetes (not exceeding 25 years) and hypertension (SBP ≥130 mm Hg and/or DBP ≥85 mm Hg) but with normo-albuminuria (urinary albumin excretion rate of <20 mcg/minute)	N=1,204 3.6 years (median)	Primary: Development of persistent microalbuminuria comparing combination therapy to placebo, acceleration factor Secondary: Primary end point comparing trandolapril and verapamil monotherapy to placebo, blood pressure, adverse events	Primary: The primary outcome was reached in 5.7% of patients receiving combination therapy versus 10.0% for patients receiving placebo (no *P* value reported). The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (*P*=0.01). Secondary: The primary outcome was reached in 6.0% of patients receiving trandolapril, 11.9% receiving verapamil and 10.0% receiving placebo (no *P* values reported). The estimated acceleration factor was 0.47 for trandolapril vs placebo (*P*=0.01) and 0.83 for verapamil vs placebo (*P*=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Throughout the study the average trough SBP/DBP was 139/80 mm Hg for patients receiving trandolapril plus verapamil, 139/81 mm Hg for trandolapril, 141/82 mm Hg for verapamil and 142/83 mm Hg for placebo. The comparison was significant (*P*≤0.002) between trandolapril plus verapamil or trandolapril alone vs placebo, but not for verapamil vs placebo. Serious adverse events were similar in all treatment groups.
Casas et al[78] ACE inhibitor or ARBs compared with placebo vs ACE inhibitor or ARBs	MA of RCT (searched up to January 2005), parallel-design Studies in adults that examined the effect of any drug	N=127 studies 4.2 years (mean)	Primary: Doubling of serum creatinine, and ESRD Secondary: Serum creatinine, urine albumin	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (*P*=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (*P*=0.04) with no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
compared with other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) Specific agents and doses were not specified.	treatment with a blood-pressure lowering action on progression of renal disease		excretion and GFR	differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (*P*=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (*P*=0.001). Compared with other drugs, ACE inhibitors or ARBs had no effect on the GFR (no *P* value reported). Conclusion: Benefits of ACE inhibitors or ARBs on renal outcomes compared with placebo are probably due to a blood-pressure lowering effect. In diabetic patients, additional renoprotective effects of ACE inhibitors or ARBs beyond blood pressure lowering remain unproven and there is uncertainty about the greater renoprotection seen in nondiabetic renal disease.
Strippoli, Craig et al[79] ACE inhibitors vs placebo (36 trials; benazepril 10 mg/day, captopril 37.5 to 100 mg/day, cilazapril* 2.5 to 5 mg/day, enalapril 5 to 40 mg/day, fosinopril 10 mg/day, imidapril* 5 mg/day, lisinopril 2.5 to 20 mg/day, perindopril 2 to 8 mg/day and ramipril 1.25 to 10.0 mg/day) or	MA of 43 RCT (to September 2003) Patients with diabetic nephropathy	N=43 trials Duration at least 6 months, range 6-63.6 months	Primary: All-cause mortality, renal outcomes (ESRD, doubling of serum creatinine, microalbuminuria to macroalbuminuria) Secondary: Not reported	Primary: ACE inhibitors significantly reduced all-cause mortality compared to placebo or no treatment (RR, 0.79; 95% CI, 0.63 to 0.99; *P*=0.04). There was a nonsignificant trend for reduction in ESRD (*P*=0.07) and doubling of serum creatinine (*P*=0.08) with ACE inhibitors compared to placebo or no treatment. ACE inhibitors significantly reduced the risk of progression from microalbuminuria to macroalbuminuria (*P*=0.0007) and increased regression back to normoalbuminuria (*P*<0.0001) compared to placebo or no treatment. ARBs did not significantly reduce all-cause mortality compared to placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17; *P*=0.95). ARBs significantly reduced the risk of ESRD (*P*=0.001) and doubling of serum creatinine (*P*=0.004). ARBs significantly decreased the risk of progression to macroalbuminuria (*P*=0.001) and increased regression to normoalbuminuria (*P*=0.02) compared to placebo or no treatment. The 3 trials that compared ACE inhibitors to ARBs did not report on all-cause mortality, ESRD or doubling of serum creatinine. Progression from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ARBs vs placebo (4 trials; irbesartan 75 to 300 mg/day [2 trials] and losartan 50 to 100 mg/day [2 trials]) or ACE inhibitors vs ARBs (3 trials; enalapril 5 to 10 mg/day vs losartan 50 mg/day [2 trials] and captopril 75 mg/day vs valsartan 80 to 160 mg/day)				microalbuminuria to macroalbuminuria was reported in 1 trial (N=92) and there was no significant difference in risk, with the point estimate favoring ACE inhibitors (RR, 0.16; 95% CI, 0.02 to 1.44; *P* value not reported). Regression from microalbuminuria to normoalbuminuria in 1 trial showed a nonsignificant difference in the risk (*P* value not reported). Secondary: Not reported
Strippoli, Bonifati et al[80] ACE inhibitors vs placebo (38 trials) or ARBs vs placebo (4 trials) or ACE inhibitors vs ARBs (7 trials)	MA of 49 RCT (to December 2005) Patients with diabetic kidney disease	N=12,067 Duration at least 6 months	Primary: All-cause mortality, ESRD, doubling of serum creatinine concentration, progression from micro- to macroalbuminuria, regression from micro- to normoalbuminuria, drug-related toxicity (including cough, headache, hyperkalemia, impotence and pedal edema) Secondary: Not reported	Primary: There was no significant difference in the risk of all-cause mortality for ACE inhibitors vs placebo or no treatment (RR, 0.91; 95% CI, 0.71 to 1.17) and ARBs vs placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17). No statistically significant reduction in the risk of all-cause mortality was found in the 3 studies that compared ACE inhibitors with ARBS (RR, 0.92; 95% CI, 0.31 to 2.78). A subgroup analysis of studies showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACE inhibitors (RR, 0.78; 95% CI, 0.61 to 0.98) but not when using half or less than half the maximum tolerable dose of ACE inhibitors (RR, 1.18; 95% CI, 0.41 to 3.44). There was a significant reduction in the risk of ESRD with ACE inhibitors and ARBS compared to placebo or no treatment (RR, 0.60; 95% CI, 0.39 to 0.93 and RR, 0.78; 95% CI, 0.67 to 0.91, respectively). There was a significant reduction in the risk of doubling of serum creatinine concentration with ACE inhibitors and ARBS (RR, 0.68; 95% CI, 0.47 to 1.00 and RR, 0.79; 95% CI, 0.67 to 0.93, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ACE inhibitors and ARBS significantly reduced the risk of progression from micro- to macroalbuminuria (RR, 0.45; 95% CI, 0.29 to 0.69 and RR, 0.49; 95% CI, 0.32 to 0.75, respectively). ACE inhibitors and ARBS significantly increased the regression from micro- to normoalbuminuria compared to placebo or no treatment (RR, 3.06; 95% CI, 1.76 to 5.35 and RR, 1.42; 95% CI, 1.05 to 1.93, respectively). The 7 studies that compared ACE inhibitors to ARBS did not report the outcome of ESRD or doubling of serum creatinine. Progression from micro- to macroalbuminuria and from micro- to normoalbuminuria were evaluated each in 1 trial and showed a nonsignificant difference in the risk between ACE inhibitors and ARBS. ACE inhibitors were associated with a significant increase in the risk of cough but not hyperkalemia, headache or impotence when compared to placebo or no treatment. ARBS were associated with a significant increase in the risk of hyperkalemia but not cough or headache compared to placebo or no treatment. Secondary: Not reported

*Product not available in the United States
Drug regimen abbreviations: BID=twice daily, Q AM=every morning, QD=once daily, SR=sustained-release, TID=three times daily
Study abbreviations: AC=active comparator, AHR=adjusted hazard ratio, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ARB=angiotensin II receptor antagonist, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, DBP=diastolic blood pressure, ECG=electrocardiogram, ESRD=end-stage renal disease, GFR=glomerular filtration rate, HDL-C=high-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, MAP=mean arterial pressure, NIDDM=non-insulin dependent diabetes mellitus, NYHA=New York Heart Association, PCI=percutaneous coronary intervention, PVD=peripheral vascular disease, SBP=systolic blood pressure, TIA=transient ischemic attack

Additional Evidence

Dose Simplification
A study by Whelton et al[64] found patients treated with lisinopril once-daily showed significantly greater reductions in systolic (P=0.023) and diastolic (P=0.007) blood pressures measured by 24-hour ambulatory blood pressure monitoring compared with patients treated with twice-daily captopril. Doses ranged from 10 to 40 mg once daily for lisinopril and from 25 to 100 mg twice daily for captopril.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity Angiotensin-Converting Enzyme Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
benazepril	tablet	Lotensin®*	$$	$
captopril	tablet	Capoten®*	$-$$	$
enalapril	tablet	Vasotec®*	$$$	$
enalaprilat dihydrate	injection	Vasotec®*†	N/A	$$
fosinopril	tablet	Monopril®*	$$$	$$
lisinopril	tablet	Prinivil®*, Zestril®*	$$$	$
moexipril	tablet	Univasc®*	$$	$$
perindopril	tablet	Aceon®	$$$	N/A
quinapril	tablet	Accupril®*	$$	$
ramipril	capsule, tablet	Altace®*	$$$	$$$
trandolapril	tablet	Mavik®*	$	$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

The therapeutic class called the single entity angiotensin-converting enzyme (ACE) inhibitors is composed of 10 unique chemical entities, all of which are available generically with the exception of perindopril. All of the agents in this class are Food and Drug Administration (FDA) approved for the treatment of hypertension, and most agents are also approved for the treatment of heart failure. Evidence-based guidelines recognize the important role that ACE inhibitors play in the treatment of hypertension and other cardiovascular and renal diseases. ACE inhibitors are recommended as a first-line option for patients with hypertension complicated by comorbidities, such as cerebrovascular disease, chronic kidney disease (of diabetic or nondiabetic origin), diabetes, heart failure, and myocardial infarction. ACE inhibitors are also recommended as first-line agents for patients with acute myocardial infarction, diabetic nephropathy, heart failure, and left ventricular dysfunction unless otherwise contraindicated. The current treatment guidelines do not establish a preference for one ACE inhibitor over another.

The ACE inhibitors have been shown to reduce morbidity and mortality in patients with and without hypertension. Based upon the results of the EUROPA trial, perindopril received FDA approval to reduce the risk of cardiovascular mortality and nonfatal myocardial infarction in patients with stable coronary artery diasease.[38] In the HOPE trial, ramipril reduced the risk of myocardial infarction, stroke and death from cardiovascular causes in patients 55 years and older who were at high risk of developing a major cardiovascular event and subsequently received FDA approval for this indication.[41] The SAVE trial also demonstrated a reduction in cardiovascular morbidity and mortality with captopril when compared to placebo in patients who had survived a myocardial infarction and had left ventricular dysfunction without overt heart failure.[47]

Although pharmacokinetic and pharmacodynamic differences exist between ACE inhibitors, the clinical relevance of these differences has not been established. A limited number of studies have been conducted comparing the single entity ACE inhibitors at adequate doses and duration to one another. Comparative data regarding the ACE inhibitors has not demonstrated distinct, clinically significant differences regarding efficacy, safety and tolerability. The consensus guidelines do not give preference to or distinguish one ACE inhibitor over another. Adverse effects common to all ACE inhibitors include dry cough, angioedema, hyperkalemia, acute renal failure and hypotension, particularly after initial doses of an ACE inhibitor in hypovolemic patients.[4]

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity angiotensin-converting enzyme inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Angiotensin-Converting Enzyme Inhibitors
Combination Products
AHFS Class 243204
September 10, 2008

I. Overview

The combination angiotensin-converting enzyme (ACE) inhibitors are products that combine an ACE inhibitor with a diuretic (hydrochlorothiazide) or a calcium-channel blocking agent (amlodipine, felodipine or verapamil) in a fixed-dose formulation. All of the combination ACE inhibitors are Food and Drug Administration (FDA)-approved for the treatment of hypertension. However, none of them are FDA approved for initial treatment of hypertension, with the exception of captopril plus hydrochlorothiazide. By combining agents from different classes, these combination products are meant to increase the effectiveness of antihypertensive therapy through complementary mechanisms of action while minimizing the potential for dose-related adverse effects.

The angiotensin-converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator.[1-3] Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system. In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption.

Hydrochlorothiazide, a thiazide diuretic, increases the excretion of sodium and chloride by inhibiting their reabsorption in the ascending loop of Henle and the early distal tubules of the kidney.[4] The exact antihypertensive mechanism of the thiazide diuretics is unknown, although sodium depletion appears to be an important factor. During initial therapy, cardiac output and extracellular volume decrease. With chronic therapy, cardiac output returns to baseline, peripheral vascular resistance falls, and there is a persistent small reduction in extracellular volume. Thiazide-type diuretics are considered initial therapy for hypertension in most patients who do not have other significant comorbid conditions.

Calcium-channel blocking agents prevent intracellular influx of calcium, causing vasodilation and decreasing the force of muscle contraction.[4] The net effect of vasodilatation is a decrease in peripheral resistance and fall in blood pressure, which results in a decrease in cardiac work. Calcium-channel blocking agents can also decrease cardiac conduction. Although these agents share the same mechanism of action, they differ in their selectivity and effects on vascular smooth muscle, myocardium, and conduction or pacemaker tissues.

Table 1 includes the combination angiotensin-converting enzyme (ACE) inhibitors included in this review. This review encompasses all dosage forms and strengths. Combination ACE inhibitors containing hydrochlorothiazide and amlodipine are available generically.

Table 1. Combination Angiotensin-Converting Enzyme Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
benazepril and amlodipine	capsule	Lotrel®*	amlodipine and benazepril
benazepril and hydrochlorothiazide	tablet	Lotensin HCT®*	benazepril and hydrochlorothiazide
captopril and hydrochlorothiazide	tablet	Capozide®*	captopril and hydrochlorothiazide
enalapril and felodipine	sustained-release tablet	Lexxel®	none
enalapril and hydrochlorothiazide	tablet	Vaseretic®*	enalapril and hydrochlorothiazide
fosinopril and	tablet	Monopril HCT®*	fosinopril and

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
hydrochlorothiazide			hydrochlorothiazide
lisinopril and hydrochlorothiazide	tablet	Prinzide®*, Zestoretic®*	lisinopril and hydrochlorothiazide
moexipril and hydrochlorothiazide	tablet	Uniretic®*	moexipril and hydrochlorothiazide
quinapril and hydrochlorothiazide	tablet	Accuretic®*	quinapril and hydrochlorothiazide
trandolapril and verapamil	extended-release tablet	Tarka®	none

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Treatment guidelines that incorporate the combination angiotensin-converting enzyme (ACE) inhibitors are summarized in Table 2. For a more comprehensive overview of the pharmacologic treatment of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Combination Angiotensin-Converting Enzyme Inhibitors

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)**[5]	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and angiotensin receptor blockers (ARBs) have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant. • The use of fixed-dose combination products was not addressed in this guideline.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[6]	• If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • The use of fixed-dose combination products was not addressed in this guideline.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of**	• Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action,

Clinical Guideline	Recommendation(s)
Hypertension (2007)[7]	there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, and the combination is likely to be well tolerated.
Treatment Guidelines From the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[8]	• Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment. • The use of fixed-dose combination products was not addressed in this guideline.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[9]	• Initial therapy in patients ≥55 years should be a calcium-channel blocking agent (CCB) or a thiazide diuretic, and in patients <55 years initial therapy should be an ACE inhibitor. If a second medication is required and the initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • The use of fixed-dose combination products was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes–2008**[10]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is >50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73m^2. • Multiple drug therapy is generally required to achieve blood pressure goals. • The use of fixed-dose combination products was not addressed in this guideline.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[11]	• All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB or ARB plus diuretic. • The use of fixed-dose combination products was not addressed in this guideline.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[12]	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence. • Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible.

III. Indications

Food and Drug Administration (FDA)-approved indications for the combination angiotensin-converting enzyme (ACE) inhibitors are noted in Table 3. Combination therapy is generally not recommended as first-line therapy for hypertension. The only agent with an FDA-approved indication for initial treatment of hypertension is captopril and hydrochlorothiazide. 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 Combination ACE Inhibitors[13-23]

Drug	Indication
Benazepril and amlodipine	Hypertension*
Benazepril and HCTZ	Hypertension*
Captopril and HCTZ	Hypertension
Enalapril and felodipine	Hypertension*
Enalapril and HCTZ	Hypertension*
Fosinopril and HCTZ	Hypertension*
Lisinopril and HCTZ	Hypertension*
Moexipril and HCTZ	Hypertension*
Quinapril and HCTZ	Hypertension*
Trandolapril and verapamil	Hypertension*

HCTZ=hydrochlorothiazide.
*This fixed-dose combination product is not indicated for the initial therapy of hypertension.

IV. Pharmacokinetics

The pharmacokinetic parameters for the combination angiotensin-converting enzyme (ACE) inhibitors are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Combination Angiotensin-Converting Enzyme (ACE) Inhibitors[4,13-24]

Drug	Bioavailability (%)	Protein Binding (%)	Elimination	Active Metabolites	Half-Life (hours)
Single Entity ACE Inhibitors					
Benazepril	≥37	~96*	Renal (20%)*****, bile (11%-12%)*****	Yes; benazeprilat	10-11*
Captopril	≥75	~25-30	Renal (>95%)	None	<2
Enalapril	~60	50-60	Renal (60%-80%), feces	Yes, enalaprilat	11*
Fosinopril	~36	~ 100*	Renal (50%), Feces (50%)	Yes, fosinoprilat	12*
Lisinopril	~25	None	Renal (100%)	None	12
Moexipril	~13	~50*	Feces (53%), renal (13%)	Yes, moexiprilat	2-9*
Quinapril	≥60	~97	Renal	Yes, quinaprilat	2*
Trandolapril	10 (70)*	80	Feces (66%), renal (33%)	Yes, trandolaprilat	6 (10)*
Single Entity Diuretics					
Hydrochlorothiazide	~50-80	68	Renal (as unchanged drug)	No	6-15
Single Entity Calcium-Channel Blocking Agents					
Amlodipine	64-90	93	Renal (10% parent, 60% inactive metabolites)	No	30-50
Felodipine	~20	>99	Renal (70%), feces (10%)	No	11-16
Verapamil	20-35	~90	Renal (~70%), feces (≥16%)	Yes, norverapamil	~12 (sustained release)

*Active metabolite.

V. Drug Interactions

Significant drug interactions with the combination angiotensin-converting enzyme (ACE) inhibitors are listed in

Table 5.

Table 5. Significant Drug-Drug Interactions for the Combination ACE Inhibitors[4]

Drug	Significance Level	Interaction	Mechanism
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	1	Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	Combining ACE inhibitors and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high-risk patients (eg, renal impairment).
Hydrochlorothiazide	1	Cisapride	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased due to electrolyte loss from thiazide diuretics.
Hydrochlorothiazide	1	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose the patient to digitalis-induced cardiac arrhythmias.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics increase potassium excretion. Hypokalemia may occur, increasing the risk of torsades de pointes. Coadministration of dofetilide and thiazide diuretics is contraindicated.
Verapamil	1	β-Blockers (acebutolol, atenolol, carteolol, esmolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol)	Verapamil may inhibit oxidative metabolism of certain β-blockers. The effects of both drugs may be increased.
Verapamil	1	Digoxin	Verapamil and digoxin have additive effects in slowing atrioventricular conduction. In addition, verapamil can increase serum concentrations of digoxin via decreased digoxin clearance. Pharmacologic effects and toxicity of digoxin may be enhanced.
Verapamil	1	Dofetilide	Verapamil can increase portal blood flow, increasing the rate of dofetilide absorption. There may be an increased risk of ventricular arrhythmias, including torsades de pointes. Coadministration is contraindicated.
Verapamil	1	Quinidine	Verapamil can prolong the half-life of quinidine by interfering with clearance. There is an increased risk for hypotension, bradycardia, ventricular tachycardia and atrioventricular block.
Verapamil	1	Ranolazine	Verapamil inhibits the metabolism (CYP3A4) of ranolazine. Ranolazine plasma levels may be elevated, increasing the risk of dose-related prolongation in the QTc interval, torsades de pointes-type arrhythmias and sudden death. Coadministration is contraindicated.
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	2	Indomethacin	Indomethacin inhibits prostaglandin synthesis. The hypotensive effect of ACE inhibitors may be reduced.
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril,	2	Lithium	Through an unknown mechanism, ACE inhibitors may increase lithium levels which results in neurotoxicity.

Drug	Significance Level	Interaction	Mechanism
trandolapril			
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	2	Salicylates (aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate)	Salicylates inhibit prostaglandin synthesis. The hypotensive and vasodilator effects of the ACE inhibitor may be reduced.
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	ACE inhibitors may temporarily increase insulin sensitivity and increase the risk of hypoglycemia.
Felodipine	2	Azole antifungals (itraconazole, ketoconazole, posaconazole, voriconazole)	Certain azole antifungals may inhibit felodipine metabolism which results in increased felodipine concentrations. Peripheral edema has been reported.
Felodipine	2	Barbiturates (amobarbital, butabarbital, butalbital, mephobarbital, pentobarbital, phenobarbital, primidone, secobarbital)	Barbiturates may increase the first-pass metabolism and decrease bioavailability of felodipine. The pharmacologic effects of felodipine may be decreased.
Felodipine	2	Carbamazepine	Carbamazepine may increase the first-pass metabolism and decrease bioavailability of felodipine. The pharmacologic effects of felodipine may be decreased.
Felodipine	2	Erythromycin	Erythromycin may inhibit the metabolism of felodipine. The pharmacologic and adverse effects of felodipine may be increased.
Felodipine	2	Grapefruit juice	Furanocoumarins present in grapefruit may inhibit the metabolism of felodipine. Serum felodipine concentrations may increase, producing an increase in pharmacologic and adverse effects. Patients taking felodipine should refrain from consuming grapefruit juice.
Felodipine	2	Hydantoins (ethotoin, fosphenytoin, phenytoin)	Hydantoins may increase the first-pass metabolism and decrease bioavailability of felodipine. The pharmacologic effects of felodipine may decrease.
Hydrochlorothiazide	2	Diazoxide	Hyperglycemia may occur with symptoms similar to diabetes. The mechanism is unknown.
Hydrochlorothiazide	2	Lithium	Thiazide diuretics decrease the renal clearance of lithium which leads to increased serum lithium levels. Lithium toxicity has occurred.
Hydrochlorothiazide	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Thiazide and loop diuretics have synergistic effects probably through a renal tubular mechanism that may result in profound diuresis and serious electrolyte abnormalities.
Hydrochlorothiazide	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion or increase potassium loss, causing hyperglycemia. Thiazide diuretics increase fasting blood glucose and may decrease sulfonylurea hypoglycemia. Hyponatremia may also occur.

Drug	Significance Level	Interaction	Mechanism
Verapamil	2	Buspirone	Verapamil may enhance the bioavailability of buspirone. The pharmacologic and adverse effects of buspirone may be increased.
Verapamil	2	Calcium salts	Calcium salts antagonize some of the effects of verapamil and the clinical effects and toxicities of verapamil may be reversed.
Verapamil	2	Carbamazepine	Verapamil appears to impair the hepatic metabolism of carbamazepine. Carbamazepine levels may increase, resulting in an increase in pharmacologic and toxic effects.
Verapamil	2	Charcoal	Charcoal will reduce the gastrointestinal absorption of orally administered verapamil and reduce its effectiveness or toxicity.
Verapamil	2	Cyclosporine	Verapamil may inhibit cyclosporine metabolism leading to increased cyclosporine levels and toxicity (eg, nephrotoxicity). However, giving verapamil before cyclosporine may be nephroprotective. The interaction is typically observed within 7 days of starting verapamil and may abate within 1 week after discontinuation.
Verapamil	2	Ethanol	Through an unknown mechanism (possibly inhibition of ethanol metabolism), verapamil may increase and prolong the central nervous system effects of ethanol affecting coordination and judgment.
Verapamil	2	Grapefruit juice	Grapefruit juice may inhibit the metabolism of verapamil. Serum verapamil concentrations may increase, producing an increase in pharmacologic and adverse effects. Avoid coadministration of verapamil with grapefruit products.
Verapamil	2	Hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Verapamil may inhibit the first-pass metabolism of certain HMG-CoA reductase inhibitors which results in increased plasma concentrations and risk of toxicity.
Verapamil	2	Macrolide antibiotics (clarithromycin, erythromycin, telithromycin)	Verapamil metabolism may be inhibited by certain macrolide antibiotics. Verapamil may increase absorption of erythromycin. Coadministration may lead to increased risk of cardiotoxicity.
Verapamil	2	Nondepolarizing muscle relaxants (atracurium, doxacurium, mivacurium, pancuronium, pipecuronium, tubocurarine, vecuronium)	The effects of the nondepolarizing muscle relaxants may be enhanced and respiratory depression may be prolonged. The mechanism probably involves blockade of calcium channels in skeletal muscle at the postsynaptic muscle membrane site.
Verapamil	2	Prazosin	Verapamil can increase serum levels of prazosin through an unknown mechanism, causing increased sensitivity to prazosin-induced postural hypotension.
Verapamil	2	Rifampin	First-pass hepatic metabolism of verapamil may be increased, resulting in lowered bioavailability and reduced effectiveness of oral verapamil.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The adverse drug event profile of the combination angiotensin-converting enzyme (ACE) inhibitors is similar to the profile of the individual components. Some side effects, however, are dose dependent and may be reduced by administration with combination therapy. For example, when benazepril is added to a regimen of amlodipine, the incidence of peripheral edema will generally be less than that seen with similar or higher doses of amlodipine monotherapy.[17] Tables 6 and 7 list the adverse reactions reported with the components of the combination ACE inhibitors. Table 8 outlines the black box warning regarding the use of ACE inhibitors during pregnancy.

Table 6. Adverse Reactions (%) Reported With the Angiotensin-Converting Enzyme (ACE) Inhibitors[4]

Adverse Event	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Moexipril	Quinapril	Trandolapril
Cardiovascular								
Angina	<1	0.2-0.3	1.5	0.2-1.0	-	<1	<0.5	-
Bradycardia	-	-	0.5-1.0	0.4-1.0	0.3-1.0	-	-	0.3-4.7
Cardiac arrest	-	✔	0.5-1.0	✔	0.3-1.0	-	-	-
Cerebrovascular accident	-	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	<0.5	-
Chest pain	-	1	2.1	0.2-2.2	3.4	>1	2.4	0.3-1.0
Hypotension	0.3	✔	0.9-6.7	0.2-4.4	1.2-9.7	0.5	2.9	0.3-1.1
Myocardial infarction	-	0.2-0.3	0.5-1.2	0.2-1.0	0.3-1.0	<1	<0.5	-
Orthostatic hypotension	0.4	✔	1.2-2.2	≤1.2-1.9	0.3-1.2	0.51	<0.5	-
Palpitations	<1	1	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.5-1.0	0.3-1.0
Peripheral edema	<1	-	-	-	0.3-1.0	>1	-	-
Rhythm disturbances	-	✔	0.5-1.0	≤0.2-1.4	-	<1	<0.5	-
Tachycardia	-	1	0.5-1.0	0.4-1.0	0.3-1.0	-	0.5-1.0	-
Central Nervous System								
Anxiety	<1	-	-	-	-	<1	-	0.3-1.0
Ataxia	-	✔	0.5-1.0	-	0.3-1.0	-	-	-
Depression	-	✔	0.5-1.0	0.4-1.0	-	-	0.5-1.0	-
Dizziness	3.6	-	0.5-7.9	1.6-11.9	5.4-11.8	4.3	3.9-7.7	1.3-23.0
Fatigue	2.4	-	0.5-3.0	≥1	2.5	2.4	2.6	-
Headache	6.2	-	1.8-5.2	≥1	4.4-5.7	>1	1.7	-
Insomnia	<1	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.5-1.0	0.3-1.0
Malaise	-	-	-	-	0.3-1.0	<1	0.5-1.0	-
Nervousness	<1	✔	0.5-1.0	-	0.3-1.0	<1	0.5-1.0	-
Paresthesias	<1	-	0.5-1.0	0.2-1.0	0.3-1.0	-	0.5-1.0	0.3-1.0
Peripheral edema	<1	-	-	-	-	>1	-	-
Somnolence/drowsiness	1.6	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.5-1.0	0.3-1.0
Vertigo	-	-	1.6	0.2-1.0	0.2	-	0.5-1.0	0.3-1.0
Dermatologic								
Alopecia	<1	-	0.5-1.0	-	0.3-1.0	<1	0.5-1.0	-

Adverse Event	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Moexipril	Quinapril	Trandolapril
Diaphoresis	<1	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.5-1.0	-
Erythema multiforme	-	✔	0.5-1.0	-	-	-	-	-
Exfoliative dermatitis	-	✔	0.5-1.0	✔	-	-	<0.5	-
Flushing	<1	0.2-0.5	0.5-1.0	0.2-1.0	0.3-1.0	1.6	-	0.3-1.0
Pemphigus/pemphigoid	<1	✔	0.5-1.0	-	0.3-1.0	-	0.5-1.0	0.3-1.0
Photosensitivity	<1	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	<0.5	-
Pruritus	<1	2	0.5-1.0	0.2-1.0	-	<1	0.5-1.0	0.3-1.0
Rash	<1	4-7	0.5-1.4	0.2-1.0	0.01-1.7	1.6	1.4	0.3-1.0
Stevens-Johnson syndrome	<1	✔	0.5-1.0	-	rare	-	-	-
Toxic epidermal necrolysis	-	-	0.5-1.0	-	rare	-	-	-
Urticaria	-	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	<1	-
Gastrointestinal								
Abdominal pain	-	-	1.6	0.2-1.0	2.2	<1	1	0.3-1.0
Anorexia	-	-	0.5-1.0	-	-	-	-	-
Constipation	<1	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.5-1.0	0.3-1.0
Diarrhea	-	-	1.4-2.1	>1	2.7-3.7	3.1	1.7	0.3-1.0
Dry mouth	-	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	0.5-1.0	-
Dysgeusia	-	2-4	-	-	-	-	-	-
Dyspepsia	-	✔	0.5-1.0	-	0.3-1.0	>1	<0.5	0.3-6.4
Hepatitis	-	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	<0.5	-
Nausea	1.3	-	1.3-1.4	1.2-2.2	2	>1	2.4	-
Pancreatitis	<1	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	<0.5	0.3-1.0
Vomiting	<1	-	1.3	1.2-2.2	0.3-1.1	<1	2.4	0.3-1.0
Genitourinary								
Decreased libido	<1	-	-	0.2-1.0	0.4	-	-	0.3-1.0
Impotence	<1	✔	0.5-1.0	-	1	-	0.5-1.0	0.3-1.0
Oliguria	-	0.1-0.2	0.5-1.0	-	0.3-1.0	<1	-	-
Urinary tract infection	<1	-	1.3	-	0.3-1.0	-	0.5-1.0	-
Musculoskeletal								
Arthralgia	<1	✔	✔	0.2-1.0	0.3-1.0	<1	0.5-1.0	-
Arthritis	<1	-	✔	✔	0.3-1.0	-	-	-
Muscle cramps	-	-	0.5-1.0	0.2-1.0	0.5	-	-	0.3-1.0
Myalgia	<1	✔	✔	0.2-1.0	0.3-1.0	1.3	-	4.7
Respiratory								
Asthma	<1	✔	0.5-1.0	-	0.3-1.0	-	-	-
Bronchitis	<1	-	1.3	-	0.3-1.0	-	-	-
Bronchospasm	-	✔	0.5-1.0	0.2-1.0	0.3-1.0	<1	-	-

Adverse Event	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Moexipril	Quinapril	Trandolapril
Cough	1.2	0.5-2.0	1.3-2.2	2.2-9.7	0.5-3.5	6.1	2.0-4.3	1.9-35
Dyspnea	<1	-	1.3	≥1	0.3-1.0	<1	-	0.3-1.0
Pharyngitis	-	-	-	0.2-1.0	0.3-1.0	1.8	0.5-1.0	-
Rhinitis	-	✔	-	0.2-1.0	0.3-1.0	>1	-	-
Sinusitis	<1	-	-	0.2-1.0	0.3-1.0	>1	-	-
Upper respiratory tract infection	-	-	0.5-1.0	2.2	1.5-2.1	>1	-	0.3-1.0
Miscellaneous								
Anemia	✔	≤0.2	-	✔	0.3-1.0	<1	<0.5	-
Angioedema	0.5	0.1	✔	0.2-1.0	0.1	<1	0.1	0.1
Asthenia	<1	✔	1.1-1.6	-	1.3	-	-	3.3
Blurred vision	-	✔	0.5-1.0	-	0.3-1.0	-	-	-
Eosinophilia	-	✔	✔	✔	0.3-1.0	-	-	-
Fever	-	✔	0.5-1.0	0.4-1	0.3-1.0	-	-	-
Syncope	0.1	✔	0.5-2.2	0.2-1.0	0.3-1.8	0.5	0.5-1.0	5.9
Tinnitus	-	-	0.5-1.0	0.2-1.0	0.3-1.0	<1	-	-
Vasculitis	-	✔	✔	-	0.3-1.0	-	-	-

- Event not reported or incidence <1%.
✔ Percent not specified.

Table 7. Adverse Drug Events (%) Associated With Amlodipine, Felodipine, Hydrochlorothiazide and Verapamil[4,24]

Adverse Event	Amlodipine	Felodipine	Hydrochlorothiazide	Verapamil
Cardiovascular				
Angina	-	0.5-1.5	-	≤1
Arrhythmia	≤1	0.5-1.5	-	-
Atrial fibrillation	≤1	-	-	-
Atrioventricular block	-	-	-	0.8-1.7
Bradycardia	≤1	-	-	1.4
Cardiac failure	✔	-	-	-
Chest pain	≤1	0.5-1.5	-	≤1
Congestive heart failure	-	-	-	1.8
Edema	1.8-14.6	-	-	1.7-3.0
Electrocardiogram abnormalities	-	-	-	2
Facial edema	-	0.5-1.5	-	-
Hypertension	-	-	-	1.7
Hypotension	≤1	0.5-1.5	1-10	0.7-2.5
Myocardial infarction	-	0.5-1.5	-	≤1
Palpitations	0.7-4.5	0.4-2.5	-	≤1
Peripheral edema	-	2.0-17.4	-	3.7
Syncope	≤1	0.5-1.5	-	≤1
Tachycardia	≤1	0.5-1.5	-	1 (severe)
Vasculitis	≤1	-	-	≤1
Ventricular extrasystoles	≤0.1	-	-	-
Ventricular tachycardia	≤1	-	-	-
Central Nervous System				
Abnormal dreams	≤1	-	-	-
Amnesia	≤0.1	-	-	-
Anxiety	≤1	0.5-1.5	-	-
Asthenia	1-2	2.2-3.9	-	2
Ataxia	≤0.1	-	-	-
Confusion	-	-	-	≤1
Depression	≤1	0.5-1.5	-	✔
Dizziness	≤3.4	2.7-3.7	-	3.0-4.7
Equilibrium disturbances	-	-	-	≤1
Fatigue	4.5	-	-	1.7-4.5
Headache	7.3	10.6-14.7	-	2.2-12.1
Hypesthesia	≤1	-	-	-
Insomnia	≤1	0.5-1.5	-	≤1
Malaise	≤1	-	-	-
Migraine	≤0.1	-	-	-
Nervousness	≤1	0.5-1.5	-	-
Paresthesia	≤1	1.2-1.6	-	≤1
Restlessness	-	-	✔	-
Shakiness/jitteriness	-	-	-	≤1
Sleep disturbances	-	-	-	1.4
Somnolence	1.3-1.6	0.5-1.5	-	≤1
Tremor	≤1	-	-	-
Vertigo	≤1	-	-	✔
Weakness	-	-	✔	-
Dermatologic				
Alopecia	≤0.1	-	<1	≤1.0
Bruising	-	-	-	≤1
Dermatitis	≤0.1	-	-	-

Adverse Event	Amlodipine	Felodipine	Hydrochlorothiazide	Verapamil
Erythema multiforme (including Stevens- Johnson syndrome)	≤1	-	<1	≤1
Exfoliative dermatitis (including toxic epidermal necrolysis)	-	-	<1	-
Flushing	-	-	-	0.6
Hair loss	≤0.1	-	-	-
Leukocytoclastic vasculitis	-	0.5	-	-
Photosensitivity	-	-	1-10	-
Pruritus	1-2	-	-	-
Rash	1-2	0.2-2.0	-	≤2.4
Rash maculopapular	≤1	-	-	-
Urticaria	≤0.1	0.5-1.5	-	≤1
Gastrointestinal				
Abdominal pain	1.6	0.5-1.5	-	-
Acid regurgitation	-	0.5-1.5	-	-
Anorexia	≤1	-	1-10	-
Appetite increase	≤0.1	-	-	-
Constipation	≤1	0.3-1.5	-	3.9-11.7
Cramping	-	-	✔	-
Diarrhea	≤1	0.5-1.5	-	≤2.4
Dry mouth	≤1	0.5-1.5	-	≤1
Dysgeusia	≤0.1	-	-	-
Dyspepsia	1-2	0.5-3.9	-	2.5-2.7
Dysphagia	≤1	-	-	-
Epigastric distress	-	-	1-10	-
Flatulence	≤1	0.5-1.5	-	-
Gastric irritation/distress	≤0.1	-	✔	≤1
Gingival hyperplasia	≤1	<0.5	-	≤1
Hepatic function impairment	-	-	✔	-
Jaundice	✔	-	✔	-
Nausea	2.9	1.0-1.7	-	1.7-2.7
Pancreatitis	✔	-	<1	-
Sialadenitis	-	-	✔	-
Thirst	≤1	-	-	-
Vomiting	≤1	0.5-1.5	-	-
Genitourinary				
Decreased libido	-	0.5-1.5	-	-
Dysuria	≤0.1	0.5-1.5	-	-
Gynecomastia	-	0.5-1.5	-	-
Impotence	-	0.5-1.5	-	≤1
Interstitial nephritis	-	-	<1	-
Nocturia	≤1	-	-	-
Polyuria	≤1	0.5-1.5	-	-
Renal dysfunction	-	-	✔	-
Renal failure	-	-	<1	-
Sexual difficulties	≤2	-	-	-
Urinary frequency	≤1	0.5-1.5	-	≤1
Hematologic				
Agranulocytosis	-	-	✔	-
Anemia	-	0.5-1.5	-	-
Aplastic anemia	-	-	<1	-
Ecchymosis	-	-	-	≤1

Adverse Event	Amlodipine	Felodipine	Hydrochlorothiazide	Verapamil
Hemolytic anemia	-	-	<1	-
Leukopenia	≤1	-	<1	-
Purpura	≤1	-	-	≤1
Thrombocytopenia	≤1	-	<1	-
Hypersensitivity				
Allergic myocarditis	-	-	<1	-
Allergic reactions (including anaphylactic shock/reaction)	✔	-	<1	-
Allergy aggravated	-	-	-	≤2
Fever	-	-	✔	-
Necrotizing angiitis	-	-	✔	-
Purpura	-	-	✔	-
Respiratory distress (including pneumonitis and pulmonary edema)	-	-	<1	1.8
Urticaria	-	-	✔	-
Metabolic				
Alanine aminotransferase increased	-	0.5-1.5	-	-
Glycosuria	-	-	✔	-
Hypercalcemia	-	-	<1	-
Hyperglycemia	≤1	-	✔	-
Hyperuricemia	-	-	✔	-
Hypokalemia	-	-	1-10	-
Liver enzymes elevated	✔	-	-	1.4
Musculoskeletal				
Arthralgia	≤1	0.5-1.5	0.5-1.5	≤1
Back pain	≤1	0.5-1.5	-	-
Hypertonia	≤0.1	-	-	-
Leg pain	-	0.5-1.5	-	-
Muscle cramps	1-2	0.5-1.5	-	≤1
Muscle spasm	-	-	✔	-
Myalgia	≤1	0.5-1.5	-	1.1
Rigors	≤1	-	-	-
Sweating	≤1	-	-	≤1
Respiratory				
Bronchitis	-	0.5-1.5	-	-
Cough	≤0.1	0.8-1.7	-	-
Dyspnea	1-2	0.5-1.5	-	1.4
Epistaxis	≤1	0.5-1.5	-	-
Pharyngitis	-	0.5-1.5	-	3
Respiratory failure	-	-	-	✔ (low frequency)
Rhinitis	≤0.1	-	-	2.7
Rhinorrhea	-	0.2-1.6	-	-
Sinusitis	-	0.5-1.5	-	3
Sneezing	-	≤1.6	-	-
Upper respiratory infection	-	0.7-3.9	-	-
Special Senses				
Abnormal/transient blurred vision	≤1	✔	✔	≤1
Conjunctivitis	≤1	-	-	-
Eye pain	≤1	-	-	-
Tinnitus	≤1	-	-	≤1
Xanthopsia	-	-	✔	-
Miscellaneous				

Adverse Event	Amlodipine	Felodipine	Hydrochlorothiazide	Verapamil
Accidental injury	-	-	-	1.5
Angioedema	≤1	0.5-1.5	-	-
Contusion	-	0.5-1.5	-	-
Flu-like illness/ syndrome/symptoms	-	0.5-1.5	-	3.7
Flushing	0.7-4.5	3.9-6.9	-	0.6-0.8
Infection	-	-	-	12.1
Pain (non-specific)	≤1	-	-	-
Warm sensation	-	≤1.5	-	-
Weight gain	≤1	-	-	-

-Event not reported or incidence <1%.
✓ Percent not specified.

Table 8. Black Box Warning for ACE Inhibitors and Use in Pregnancy

Warning for Use in Pregnancy
CONTRAINDICATION
When used in pregnancy during the second and third trimesters, angiotensin-converting enzyme (ACE) inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, the ACE inhibitor should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

VII. Dosing and Administration

The usual dosing regimens for the combination angiotensin-converting enzyme (ACE) inhibitors are summarized in Table 9. Captopril and hydrochlorothiazide is the only combination ACE inhibitor Food and Drug Administration (FDA)-approved for use as an initial agent. All other agents are recommended for use after the patient has failed to achieve the desired antihypertensive effect and/or experienced unacceptable side effects on monotherapy with one of the principal components. Combination therapy may be initiated after failure on monotherapy or substituted for the titrated individual components.

Table 9. Usual Dosing for the Combination Angiotensin-Converting Enzyme Inhibitors[13-23]

Drug	Usual Adult Dosage	Usual Pediatric Dosage	Availability
Benazepril and amlodipine	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Capsule: 10 mg-2.5 mg 10 mg-5 mg 20 mg-5 mg 20 mg-10 mg 40 mg-5 mg 40 mg-10 mg
Benazepril and HCTZ	Hypertension: Fixed-combination drug is not indicated for initial therapy; switch to 10 mg-12.5 mg or 20 mg-12.5 mg per day if not adequately controlled on benazepril monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 5 mg-6.25 mg 10 mg-12.5 mg 20 mg-12.5 mg 20 mg-25 mg
Captopril and HCTZ	Hypertension: Initial: 25 mg-5 mg once daily; titrate with individual components or fixed-combination; combination may be substituted for the titrated individual components; in general, daily doses of captopril and HCTZ should not exceed 150 mg and 50 mg, respectively	Safety and efficacy in children have not been established.	Tablet: 25 mg-15 mg 25 mg-25 mg 50 mg-15 mg 50 mg-25 mg
Enalapril and felodipine	Hypertension: Fixed-combination drug is not indicated for initial	Safety and efficacy in children have not	Tablet, sustained-release:

Drug	Usual Adult Dosage	Usual Pediatric Dosage	Availability
	therapy; initiate combination therapy after failure on monotherapy, initially 1 tablet daily; dose may be increased to 2 tablets once daily if blood pressure control is inadequate after 1 to 2 weeks; combination may be substituted for the titrated individual components (although the felodipine component of Lexxel® has not been shown to be bioequivalent to Plendil®)	been established.	5 mg-5 mg
Enalapril and HCTZ	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum: 4 tablets of 5 mg-12.5 mg or 2 tablets of 10 mg-25 mg	Safety and efficacy in children have not been established.	Tablet: 5 mg-12.5 mg 10 mg-25 mg
Fosinopril and HCTZ	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect	Safety and efficacy in children have not been established.	Tablet: 10 mg-12.5 mg 20 mg-12.5 mg
Lisinopril and HCTZ	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy on 10 mg-12.5 mg or 20 mg-12.5 mg after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; maximum: lisinopril 80 mg and HCTZ 50 mg per day	Safety and efficacy in children have not been established.	Tablet: 10 mg-12.5 mg 20 mg-12.5 mg 20 mg-25 mg
Moexipril and HCTZ	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy on 7.5 mg-12.5 mg, 15 mg-12.5 mg or 15 mg-25 mg after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; maximum: lisinopril 30 mg and HCTZ 50 mg per day	Safety and efficacy in children have not been established.	Tablet: 7.5 mg-12.5 mg 15 mg-12.5 mg 15 mg-25 mg
Quinapril and HCTZ	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy on 10 mg-12.5 mg or 20 mg-12.5 mg after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 10 mg-12.5 mg 20 mg-12.5 mg 20 mg-25 mg
Trandolapril and verapamil	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; clinical trials only evaluated once-a-day doses (usual dosage range for trandolapril for hypertension is 1-4 mg per day in 1or 2 divided doses and for verapamil extended-release 120 to 480 mg per day in 1 or 2 divided doses)	Safety and efficacy in children have not been established.	Tablet, extended-release: 1 mg-240 mg 2 mg-180 mg 2 mg-240 mg 4 mg-240 mg

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the combination angiotensin-converting enzyme (ACE) inhibitors are summarized in Table 10.

Table 10. Comparative Clinical Trials Using the Combination Angiotensin-Converting Enzyme (ACE) Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Messerli, Weiret al [25] Amlodipine/benazepril 5/10 mg/day or 5/20 mg/day	OL, RCT Patients ≥18 years with mild-to-moderate hypertension currently taking amlodipine 5 or 10 mg with inadequate blood pressure control (DBP ≥90 mm Hg, Group 1) or inability to tolerate amlodipine (DBP ≤90 mm Hg but with edema, Group 2)	N=7,912 4 weeks	Primary: Group 1-change in mean sitting DBP Group 2-percentage of patients whose edema improved Secondary: Group 1-change in mean sitting SBP	Primary: In Group 1, mean reduction in DBP at week 4 was 11.5 mm Hg (95% CI, –11.8 to –11.3 mm Hg; *P*<0.001). Mean DBP declined from 96.5 (baseline) to 84.9 mm Hg (at 4 weeks). In Group 2, 85% of patients saw improvement in edema with 42% of patients experiencing complete resolution after receiving combination therapy (95% CI, 83% to 87%; no *P* value reported). Secondary: In Group 1, mean reduction in SBP at week 4 was 15.6 mm Hg (95% CI, –16.0 to –15.2 mm Hg; *P*<0.001).
Messerli, Oparil et al[26] Study 1: Nifedipine 30 to 60 mg/day vs amlodipine/benazepril 5/10 mg/day-5/20 mg/day Study 2:	Two DB, MC, RCT Patients with uncomplicated essential hypertension who were 18-80 years of age	N=1,079 8 weeks	Primary: Change in DBP from baseline Secondary: Change from baseline in SBP and heart rate	Primary: Study 1 Significant reductions in DBP were observed with amlodipine/benazepril 5/10 mg and 5/20 mg (–9.4 and –9.7 mm Hg, respectively) compared to nifedipine 30 mg (–7.0 mm Hg; *P*<0.05) but not nifedipine 60 mg (–8.5; *P*>0.05). Study 2 Amlodipine/benazepril 5/10 mg (–8.9 mm Hg) and 5/20 mg (–9.1 mm Hg) produced significantly greater reductions in DBP than amlodipine 5 mg (–6.8 mm Hg; *P*<0.05) but not amlodipine 10 mg (–8.7 mm Hg; *P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Amlodipine 5 to 10 mg/day vs amlodipine/benazepril 5/10 mg/day-5/20 mg/day				Secondary: Study 1 Significant reductions in SBP were observed only with amlodipine/benazepril 5/20 (–11.6 mm Hg) compared to nifedipine 30 mg (–7.9 mm Hg; *P*<0.05). Significantly less edema was reported with combination therapies (3.1% to 3.8%; *P*≤0.001) than nifedipine 60 mg (15.5%; *P*=0.008) but not nifedipine 30 mg (5.4%). Study 2 Significant reductions in SBP were observed only with amlodipine/benazepril 5/20 mg (–9.1 mm Hg) compared to amlodipine 5 mg (–5.3 mm Hg, *P*<0.05). There were no significant difference in SBP between amlodipine 10 mg and the combination therapies. Significantly less edema (*P*<0.001) was reported with amlodipine 5 mg (4.9%) and combination therapies (1.5% to 2.2%) compared to amlodipine 10 mg (23.6%).
Jamerson et al [27] Amlodipine/benazepril 5/20 mg-10/20 mg/day (fixed-dose combination) vs amlodipine 5 to 10 mg/day	DB, MC, PG, RCT Men and women 18-80 years with stage 2 hypertension	N=364 12 weeks	Primary: Percentage of patients with SBP reduction ≥25 mm Hg (if baseline <180 mm Hg) or ≥32 mm Hg (if baseline ≥180 mm Hg) Secondary: Percentage of patients with DBP ≥15 mm Hg (if baseline <110 mm Hg) or ≥20 mm Hg (if baseline ≥110 mm Hg),	Primary: Significantly more patients on combination therapy (74.2%) met the primary end point than with amlodipine monotherapy (53.9%; *P*<0.0001). The time by which 50% of patients attained the primary end point was 4 weeks shorter among patients randomized to combination therapy compared with those randomized to monotherapy (*P*<0.0001). Secondary: Significantly more patients on combination therapy met the DBP end point than amlodipine monotherapy (67.0% vs 48.3%; *P*=0.0003). Patients on combination therapy had significantly greater mean SBP reductions (–25.5 vs –20.5 mm Hg; *P*=0.0003) and DBP reductions (–14.3 vs –10.4 mm Hg; *P*=0.0001) than amlodipine monotherapy. Significantly more patients on combination therapy met the blood pressure goal of <140/90 mm Hg than amlodipine monotherapy (61.0% vs 43.3%; *P*=0.0007).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			percentage of patients meeting goal of 140/90 mm Hg and ≤130/85 mm Hg, mean reduction in SBP and DBP and incidence of edema	Significantly more patients on combination therapy met the blood pressure goal of <130/85 mm Hg than amlodipine monotherapy (35.7% vs 19.1%; *P*=0.0004). The incidence of peripheral edema was significantly higher in the amlodipine monotherapy group (23.3% vs 12.6%; *P*=0.0102). There was no significant difference in the incidence of other adverse events.
Neutel et al[28] SELECT Amlodipine and benazepril 5/20 mg/day vs amlodipine 5 mg/day vs benazepril 20 mg/day	DB, RCT Patients with stage 2 systolic hypertension	N=443 8 weeks	Primary: Reduction in SBP, proportion of patients achieving blood pressure control Secondary: Not reported	Primary: Significantly greater SBP reductions were achieved with combination treatment compared to amlodipine or benazepril monotherapy (*P*<0.0001). Significantly more patients on combination therapy met blood pressure goals than on monotherapy (*P*<0.0001). No significant difference was noted in the incidence of adverse events. Adverse events were low in all 3 treatment arms, with less peripheral edema in the combination group than in the amlodipine-treated group. Secondary: Not reported
Kuschnir et al[29] Amlodipine/benazepril 5/20 mg/day (fixed-dose combination) vs amlodipine 5 mg/day vs benazepril 20 mg/day	DB, MC, PC, PG, RCT Men and women 21 to 80 years of age with uncomplicated primary hypertension	N=308 8 weeks	Primary: Reduction in mean sitting DBP, SBP and percentage of patients with DBP <90 mm Hg or ≥10 mm Hg reduction Secondary: Not reported	Primary: All treatment groups significantly reduced mean sitting DBP compared to placebo (*P*<0.001). Combination amlodipine/benazepril had significantly greater reductions in DBP (–13.2 mm Hg; *P*<0.001) compared to amlodipine (–8.8 mm Hg) and benazepril (–6.7 mm Hg) monotherapy. Combination amlodipine/benazepril had significantly greater reductions in SBP (–24.7 mm Hg; *P*<0.001) compared to amlodipine (–16.2 mm Hg) and benazepril (–12.4 mm Hg). Significantly more patients on combination amlodipine/benazepril

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				reached DBP <90 mm Hg or ≥10 mm Hg reduction (87.0%; *P*≤0.005) compared to amlodipine (67.5%) and benazepril (53.3%). Adverse events considered to be drug related occurred in 15.6% of patients receiving amlodipine/benazepril, 24.7% of patients receiving amlodipine, 6.5% of patients on benazepril and 11.7% of patients on placebo (no *P* values reported). Secondary: Not reported
Chrysant, Sugimoto et al[30] Amlodipine/benazepril 10/40 mg/day for 6 weeks vs amlodipine/benazepril 10/40 mg/day for 2 weeks with forced titration to 20/40 mg/day for 4 weeks vs amlodipine 10 mg/day for 6 weeks	DB, MC, RCT Men and women ≥18 years with mean sitting DBP ≥95 mm Hg not adequately controlled with amlodipine 10 mg/day monotherapy	N=812 6 weeks	Primary: Reduction in mean sitting DBP and SBP, reductions in ambulatory blood pressure, successful response (mean sitting DBP <90 mm Hg or decrease of ≥10 mm Hg from baseline), safety Secondary: Not reported	Primary: Treatment with amlodipine/benazepril 10/40 mg and 10/20 mg resulted in a decrease of mean sitting SBP and DBP by 13.3/12.7 and 12.1/11.6 mm Hg, respectively, compared with monotherapy (6.6/8.5 mm Hg; *P*<0.0001). Amlodipine/benazepril 10/40 mg and 20/40 mg decreased ambulatory SBP and DBP by 9.9/6.7 and 7.4/5.2 mm Hg, respectively, compared with monotherapy (*P*<0.0001). Both combinations resulted in more responders than monotherapy (74% and 65% vs 54%; *P*<0.0001 and *P*<0.0085, respectively). Combination amlodipine and benazepril had significantly greater reductions in sitting SBP (–17 mm Hg; *P*<0.0001) compared to amlodipine monotherapy (–5 mm Hg). The incidence of pedal edema was lower but not significantly different in the amlodipine/benazepril combinations compared with monotherapy (4.5%, 5.5% vs 9.2%, respectively; *P*=NS). No significant metabolic side effects were noted among the combination groups. Secondary: Not reported
Chrysant, Bakris et al[31] Amlodipine/benazepril 5/40 mg/day for 4	DB, RCT Men and women (mean age 53	N=329 8 weeks	Primary: Reduction in mean sitting DBP and SBP, reduction in	Primary: Combination amlodipine and benazepril had significantly greater reductions in sitting SBP (–17 mm Hg; *P*<0.0001) compared to benazepril monotherapy (–5 mm Hg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks with forced titration to 10/40 mg/day for an additional 4 weeks vs benazepril 40 mg/day for 8 weeks	years) with mean sitting DBP ≥95 mm Hg not adequately controlled with benazepril 40 mg/day monotherapy		standing DBP and SBP, and change in heart rate, safety Secondary: Not reported	Combination amlodipine and benazepril had significantly greater reductions in sitting DBP (–14 mm Hg; *P*<0.0001) compared to benazepril monotherapy (–7 mm Hg). Combination amlodipine and benazepril had significantly greater reductions in standing SBP (–17 mm Hg; *P*<0.0001) compared to benazepril monotherapy (–6 mm Hg). Combination amlodipine and benazepril had significantly greater reductions in standing DBP (–14 mm Hg; *P*<0.0001) compared to benazepril monotherapy (–7 mm Hg). No significant differences in heart rate were observed (*P*>0.05). No significant differences in adverse events were reported (*P*>0.05). Secondary: Not reported
Fogari et al [32] Amlodipine/benazepril 2.5/10 mg/day or 5/10 mg/day vs benazepril 10 mg/day	DB, MC, PC, RCT Men and women aged 24-73 years (mean 55 years) with hypertension inadequately controlled with ACE inhibitor monotherapy	N=448 8 weeks	Primary: Reduction in mean sitting DBP Secondary: Reduction in sitting SBP, standing DBP and SBP, and percentage of patients with DBP <90 mm Hg (deemed excellent response) or ≥10 mm Hg reduction (deemed good response)	Primary: Significantly greater reductions in sitting DBP were observed with amlodipine/benazepril 2.5/10 mg (–5.3 mm Hg, 97.5% CI, –8.3 to –2.4 mm Hg; *P*=0.0001) and amlodipine/benazepril 5/10 mg (–4.5 mm Hg, 97.5% CI, –7.4 to –1.6 mm Hg; *P*=0.0006) compared to benazepril monotherapy. Secondary: Significantly greater reductions in sitting SBP were seen with amlodipine/benazepril 2.5/10 mg (–7.9 mm Hg, 97.5% CI, –12.3 to –3.5 mm Hg; *P*=0.0001) and amlodipine/benazepril 5/10 mg (–7.9 mm Hg, 97.5% CI, –12.2 to –3.6 mm Hg; *P*=0.0000) compared to benazepril monotherapy. Significantly greater reductions in standing DBP and SBP were also reported with the combination therapy compared to benazepril monotherapy (*P*≤0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significantly more patients had excellent or good response with combination amlodipine/benazepril 2.5/10 mg (69.2%; *P*=0.0004) and 5/10 mg (65.8%; *P*=0.02) compared to benazepril monotherapy (40.5%). Tolerability was good in the 3 treatment groups and no significant abnormal laboratory data was detected.
Hilleman et al[33] Amlodipine/benazepril (fixed-dose combination) vs 9 monotherapies (atenolol, hydrochlorothiazide, captopril, enalapril, lisinopril, amlodipine, diltiazem, nifedipine and verapamil)	MA of RCT (published between January 1985 and January 1998) of first-line monotherapies and the fixed-dose combination Patients with mild-to-moderate essential hypertension	82 studies enrolling ≥20 patients (total N not reported) ≥4 weeks	Primary: Absolute change in supine DBP from baseline Secondary: Percent of patients who achieved BP control, safety	Primary: The mean absolute decrease in supine DBP ranged from 9.7 to 13.3 mm Hg with verapamil showing the greatest effect and captopril the least. When studies were weighted by sample size, amlodipine/benazepril, atenolol, lisinopril, and verapamil showed the greatest blood pressure effect. Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5% to 79.0%, with amlodipine/benazepril (74.3%) and lisinopril (79.0%) showing the highest percentage control (*P*=0.096). The incidence of adverse events ranged from 12.1% to 41.8%, with lisinopril and verapamil showing the lowest incidences (12.1% and 14.1%, respectively) and nifedipine the highest incidence. Lisinopril demonstrated significantly less overall side effects compared with nifedipine (*P*=0.030). Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem (*P*=0.002). Although amlodipine/benazepril had the lowest rate of withdrawals due to adverse events, lack of significant change was due to the low number of cohorts available for analysis.
Bakris et al[34] GUARD Amlodipine/benazepril (fixed-dose combination)	DB, RCT Hypertensive, albuminuric type 2 diabetic patients, mean age 58 years were randomized to	N=322 52 weeks	Primary: Change in urinary albumin to creatinine ratio after 1 year of initial treatment with either fixed-dose combination,	Primary: Both combinations significantly reduced the urinary albumin to creatinine ratio compared to baseline (*P*<0.0001). The median percent change was –72.1% for benazepril/HCTZ and –40.5% for amlodipine/benazepril (*P*<0.0001). Both regimens significantly reduced SBP and DBP compared to baseline (*P*<0.0001). The mean reduction in both SBP and DBP was greater in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs benazepril/HCTZ (fixed-dose combination) Doses were not specified in this reference.	receive either initial fixed-dose combination product		blood pressure reductions Secondary: Proportion who progressed to overt diabetic nephropathy, safety	amlodipine-based arm than in the HCTZ-based arm; however, significance in favor of the amlodipine regimen was observed only for DBP (SBP –20.5 vs –18.8; *P*=0.19; DPB –13.1 vs –9.97; *P*=0.02). A greater proportion of patients who had microalbuminuria at baseline and treated with benazepril/HCTZ compared with amlodipine/benazepril attained normalization of the urinary albumin to creatinine ratio, defined as <30 mg/g (69.2% vs 47.8%; *P*=0.0004). Secondary: The percentage of patients progressing to overt proteinuria was similar for both groups. Overall, both study drugs were well tolerated. Adverse reactions possibly related to the study medications occurred in 11.4% and 3.6% of patients receiving amlodipine/benazepril and benazepril/HCTZ, respectively (no *P* value reported). They included peripheral edema (7.8% vs 2.4%, respectively), fatigue (1.2% in each group), pitting edema (1.2% vs 0.0%), face edema (0.6% vs 0.0%) and thirst (0.6% vs 0.0%). More patients receiving the HCTZ-based regimen (10.8%) discontinued study drug than with the amlodipine-based regimen due to side effects (5.4%; no *P* value reported).
Jamerson, Bakris et al[35] ACCOMPLISH (preliminary report on blood pressure control rates) Amlodipine/benazepril 5/40 mg per day (forced titration) vs benazepril/HCTZ 40/12.5 mg per day	DB, MC, RCT Men and women >60 years with hypertension and cardiovascular or renal disease or 2 target organs damaged by hypertension	N=10,704 Analysis performed at 6 months (complete trial duration 5 years)	Primary: Changes in mean SBP from baseline to 6 months, blood pressure control rates (SBP/DBP <140/90 mm Hg or <130/89 mm Hg for patients with diabetes and chronic kidney disease) Secondary: Not reported	Primary: At baseline, 97% of subjects were treated with antihypertensive medications at entry but only 37% of participants had blood pressure control. Mean blood pressure fell from 145/80 to 132/74 mm Hg after 6 months of treatment with either combination regimen (*P*<0.001). (This preliminary report did not compare the 2 treatment regimens.) The 6-month blood pressure control rate was 73% in the overall trial (78% in the United States), 43% in diabetics and 40% in patients with renal disease. Of the patients uncontrolled, 61% were not on maximal medications. The authors noted that the ACCOMPLISH blood pressure control rates

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(forced titration)				are the highest of any multinational trial to date. Secondary: Not reported Note: Recruitment for the ACCOMPLISH trial has been completed but the full analysis of the study has not yet been published. This trial was designed to compare the efficacy of amlodipine/benazepril to benazepril/HCTZ in preventing major clinical outcomes in hypertensive patients at high risk of cardiovascular events.
Malacco et al[36] Amlodipine/benazepril 5/10 mg/day vs captopril/HCTZ 50/25 mg/day	DB, MC, RCT Patients with mild-to-moderate arterial hypertension (sitting DBP >95 mm Hg and/or SBP >160 mm Hg) inadequately controlled by monotherapy with an ACE inhibitor, calcium-channel blocking agent or diuretic	N=397 12 weeks	Primary: Reduction in sitting DBP and SBP Secondary: Percentage of patients responding to therapy (DBP<90 mm Hg, reduction in DBP ≥10 mm Hg or SBP ≥20 mm Hg, or SBP <150 mm Hg)	Primary: Significantly lower sitting DBP (–2.7 mm Hg; *P*<0.001) and SBP (–3.7 mm Hg; *P*<0.001) were achieved with amlodipine/benazepril compared to captopril/HCTZ. Secondary: Significantly more amlodipine/benazepril patients responded to therapy (94.8%) compared to captopril/HCTZ (86.0%; *P*=0.004). No differences in adverse events were reported between the 2 treatment groups.
Kereiakes et al[37] Benazepril 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, then benazepril 20 mg/day plus amlodipine 5 mg/day for 4 weeks, then benazepril 20 mg/day plus amlodipine 10	DB, DD, MC, PG, RCT Patients with stage 2 hypertension (mean seated DBP ≥90 mm Hg but <115 mm Hg and SBP ≥160 mm Hg but <200	N=190 12 weeks	Primary: Change in mean seated SBP at the end of week 12 Secondary: DBP at the end of week 12, percent of patients attaining blood pressure goals of <140/90	Primary: Patients treated with olmesartan/HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril/amlodipine (least square mean change, –32.5 vs –26.5 mm Hg; *P*=0.024; least square mean treatment difference, –6.0 mm Hg; 95% CI, –11.1 to –0.8 mm Hg). Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan/HCTZ compared with benazepril/amlodipine at week 12 (*P*=0.056).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day for 4 weeks vs olmesartan 20 mg/day for 2 weeks, then 40 mg/day for 2 weeks then olmesartan/HCTZ 40/12.5 mg/day (fixed-dose combination) for 4 weeks increased to 40/25 mg for 4 weeks	mm Hg or DBP ≥100 mm Hg but <115 mm Hg)		mm Hg, <130/85 mm Hg, and <130/80 mm Hg	The percentage of patients achieving goal rates at the end of the study for olmesartan/HCTZ and benazepril/amlodipine were 66.3% and 44.7% (*P*=0.006) for <140/90 mm Hg, 44.9% vs 21.2% (*P*=0.001) for <130/85 mm Hg, and 32.6% and 14.1% (*P*=0.006) for <130/80 mm Hg. Both treatments were well tolerated.
Elliot et al[38] Enalapril 10 mg QD vs enalapril/felodipine ER 5/5 mg/day (fixed-dose combination) After 6 weeks, all patients received the fixed-dose combination for an additional 6 weeks.	DB, PG, PRO, RCT, partial crossover study Patients with sitting DBP >95 mm Hg and <115 mm Hg	N=217 12 weeks	Primary: Change in sitting DBP, proportion of responders (DBP <90 mm Hg or a reduction of >10 mm Hg Secondary: Not reported	Primary: Patients receiving combination therapy had significantly greater reductions in sitting SBP/DBP compared with baseline (*P*<0.05/*P*<0.01). More patients receiving combination therapy were classified as responders than patients receiving enalapril monotherapy (59% vs 41%; *P*<0.01). When patients originally taking 10 mg enalapril were crossed over to the combination therapy for an additional 6 weeks, there was a further blood pressure reduction and increase in response rate, with loss of significant differences compared with those treated continuously with the combination for the entire 12 weeks. There were no significant differences in tolerability between the regimens. Secondary: Not reported
Pepine, Handberg et al[39] INVEST Verapamil SR 240	MC, OL, RCT Men and women with essential hypertension (as defined by JNC	N=22,576 24 months	Primary: First occurrence of death (all cause), nonfatal myocardial infarction or stroke	Primary: At 24 months, in the calcium antagonist strategy (CAS) subgroup, 81.5% of patients were taking verapamil SR, 62.9% trandolapril and 43.7% HCTZ. In the non-calcium antagonist strategy (NCAS), 77.5% of patients were taking atenolol, 60.3% HCTZ and 52.4% trandolapril.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) vs atenolol 50 mg/day (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) Trandolapril was recommended for all patients with heart failure, diabetes, or renal insufficiency.	VI) and CAD, mean age 66 years		Secondary: cardiovascular death, angina, cardiovascular hospitalization, angina, blood pressure control (JNC VI goals SBP/DBP <140/90 mm Hg or <130/85 mm Hg if diabetic or renal impairment), safety	After a follow-up of 61,835 patient-years (mean, 2.7 years per patient), 2,269 patients had a primary outcome event with no statistically significant difference between treatment strategies (9.93% in CAS vs 10.17% in NCAS; RR, 0.98; 95% CI, 0.90 to 1.06; *P*=0.57). Secondary: There was no significant difference in the rate of cardiovascular death (*P*=0.94) or cardiovascular hospitalization (*P*=0.59) between the 2 treatment groups. At 24 months, angina episodes decreased in both groups, but the mean frequency was lower in the CAS group (0.77 episodes/week) compared with the NCAS group (0.88 episodes/week; *P*=0.02). Two-year blood pressure control was similar between groups. The JNC VI blood pressure goals were achieved by 65.0% (systolic) and 88.5% (diastolic) of CAS patients and 64.0% (systolic) and 88.1% (diastolic) of NCAS patients. A total of 71.7% of CAS patients and 70.7% of NCAS patients achieved an SBP <140 mm Hg and DBP <90 mm Hg. Both regimens were generally well tolerated. Patients in the CAS group reported constipation and cough more frequently than patients in the NCAS group, while NCAS patients experienced more dyspnea, lightheadedness, symptomatic bradycardia and wheezing (all were statistically significant with *P*≤0.05) .
Pepine, Kowey et al[40] INVEST (see above) Verapamil SR (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) vs	Post hoc analysis of INVEST (see above) Men and women with essential hypertension (as defined by JNC VI) and CAD, mean age 66 years	N=22,576 24 months	Primary: Risk for adverse outcome associated with baseline factors, follow-up blood pressure and drug treatments Secondary: Not reported	Primary: Previous heart failure (adjusted HR, 1.96), as well as diabetes (HR, 1.77), increased age (HR, 1.63), United States residency (HR, 1.61), renal impairment (HR, 1.50), stroke/TIA (HR, 1.43), smoking (HR, 1.41), MI (HR, 1.34), peripheral vascular disease (HR, 1.27), and revascularization (HR, 1.15) predicted increased risk. Follow-up SBP <140 mm Hg (HR, 0.82) or DBP <90 mm Hg (HR, 0.70) and trandolapril with verapamil SR (HR, 0.78 and 0.79) were associated with reduced risk. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atenolol (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4)				Not reported
Brunner et al[41] INVEST (see above) Analysis of patients randomly assigned to verapamil SR 240 mg and had trandolapril (1, 2, or 4 mg) added to their treatment because of failing to meet blood pressure goals.	Post hoc analysis of INVEST (see above) Men and women with essential hypertension (as defined by JNC VI) and CAD, mean age 66 years	N=1,832 (subset of INVEST) 24 months	Primary: Factors influencing blood pressure response to trandolapril add-on therapy Secondary: Not reported	Primary: Trandolapril decreased mean unadjusted SBP and DBP by –9.1 and –4.1 mm Hg, respectively. The percentage of patients with blood pressure under control (<140/90 mm Hg) increased from 6.7% to 41.3% (*P*<0.0001). Adjusted blood pressure response was significantly associated with age and baseline SBP and DBP (*P*<0.0001). Whereas the decrease in SBP was more pronounced in younger patients, the opposite was observed for DBP decrease. DBP response was significantly associated with race. Specifically, the adjusted DBP decrease was significantly smaller in Hispanics and African Americans than whites (*P*=0.0032 and *P*=0.0069, respectively). However, Hispanics achieved a decrease in SBP and an increase in blood pressure control similar to the other ethnic groups. Secondary: Not reported
Karlberg et al[42] Trandolapril 2 mg/day vs verapamil 240 mg/day vs trandolapril/verapamil	DB, MC, PRO, RCT, XO Patients with uncomplicated primary hypertension (sitting DBP between 95 and 115 mm Hg) between the ages	N=226 2 months	Primary: Change in blood pressure and rate pressure product Secondary: Predictive value of plasma concentrations of active renin	Primary: The mean fall in blood pressure was significantly greater with the combination (20/15 mm Hg; *P*<0.00054), as compared to both trandolapril (14/11 mm Hg) or verapamil (13/11) mm Hg. The difference between verapamil and trandolapril was not significant. Rate pressure product decreased significantly more on the combination (*P*<0.001) than on trandolapril or verapamil alone. Secondary: There was a significant positive correlation between blood pressure fall

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
2/180 mg/day (fixed-dose combination)	of 20-80 years		regarding the blood pressure response to the different treatment regimens, safety	and plasma concentrations of active renin (eg, the higher the initial active renin, the better the blood pressure response to trandolapril [*P*<0.045 for SBP and *P*<0.004 for DBP]). No relationships were found for either verapamil or the combination. All treatments were well tolerated and safe.
Ruggenenti et al[43] BENEDICT Trandolapril 2 mg/day vs verapamil SR 240 mg/day vs trandolapril/verapamil SR 2/180 mg/day (fixed-dose combination) vs placebo	DB, MC, RCT Patients ≥40 years with type 2 diabetes (not exceeding 25 years) and hypertension (SBP ≥130 mm Hg and/or DBP ≥85 mm Hg) but with normo-albuminuria (urinary albumin excretion rate of <20 µg/minute)	N=1,204 3.6 years (median)	Primary: Development of persistent microalbumin-uria comparing combination therapy to placebo, acceleration factor Secondary: Primary end point comparing trandolapril and verapamil monotherapy to placebo, blood pressure, adverse events	Primary: The primary outcome was reached in 5.7% of patients receiving combination therapy versus 10.0% for patients receiving placebo (no *P* value reported). The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (*P*=0.01). Secondary: The primary outcome was reached in 6.0% of patients receiving trandolapril, 11.9% receiving verapamil and 10.0% receiving placebo (no *P* values reported). The estimated acceleration factor was 0.47 for trandolapril vs placebo (*P*=0.01) and 0.83 for verapamil vs placebo (*P*=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Throughout the study the average trough SBP/DBP was 139/80 mm Hg for patients receiving trandolapril plus verapamil, 139/81 mm Hg for trandolapril, 141/82 mm Hg for verapamil and 142/83 mm Hg for placebo. The comparison was significant (*P*≤0.002) between trandolapril plus verapamil or trandolapril alone vs placebo, but not for verapamil vs placebo. Serious adverse events were similar in all treatment groups.
Cifkova et al[44] Verapamil SR/trandolapril 180/2	AC, OL, RCT, XO Caucasian	N=100 8 months	Primary: LDL-C Secondary:	Primary: LDL-C was not significantly different between the 2 treatment groups (*P*=0.909).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QD (VT) (fixed-dose combination) vs captopril/HCTZ 50/25 mg QD (CH) (fixed-dose combination) After 16 weeks, patients were switched to the other fixed combination for an additional 16 weeks.	patients aged 18-75 years with mild-to-moderate essential hypertension (SBP 140-209 mm Hg and DBP 90-119 mm Hg)		Other lipid parameters (HDL-C, TC, triglycerides, apolipoproteins AI and B, lipoprotein(a)), blood pressure parameters	Secondary: All secondary lipid parameters remained unaltered except for HDL-C which was significantly higher with VT (1.39 vs 1.35 mmol/L; *P*<0.03). Serum potassium declined while uric acid and glucose increased on CH (all *P*<0.001). While there were no significant differences with respect to adjusted mean DBP, adjusted mean SBP was slightly higher on treatment with VT than with CH. These differences reached statistical significance for the 24-hour and night-time means, although the absolute adjusted mean treatment differences were only 2.3 mm Hg (*P*=0.02) and 3.5 mm Hg (*P*=0.01), respectively. The number of patients who achieved DBP <90 mm Hg at the end of each treatment did not differ (56% VT vs 46% CH; *P*=NS). Heart rate was significantly lower in the VT group than the CH group (treatment differences ranged from 2.8-4.5 beats per minute; all *P*≤0.001).
Nakao et al[45] COOPERATE Trandolapril 3 mg/day vs losartan 100 mg/day vs trandolapril and losartan at equivalent doses	DB, MC, PC, RCT Patients aged 18 to 70 years with chronic nephropathy (nondiabetic renal disease)	N=263 3 years	Primary: Composite of time to doubling of serum creatinine or ESRD Secondary: Changes in blood pressure, daily urinary protein excretion, adverse effects	Primary: The combined end point was reached in 11% of patients in the combination trandolapril and losartan group compared with 23% of patients in the trandolapril (*P*=0.018) and 23% of patients in the losartan group (*P*=0.016). Secondary: Mean SBP and DBP reductions were similar among the 3 treatment groups (*P*=0.109). All patients receiving active treatment had significant decreases in urinary protein excretion, but the greatest difference was seen with the combination trandolapril and losartan group compared to trandolapril or losartan (–75.6%, –44.3% and –42.1%, respectively; *P*=0.01). The frequency of adverse events did not differ between groups, although a slightly higher occurrence of hyperkalemia and dry cough was recorded in the trandolapril and combination groups than in the losartan group (*P* value not specified).
Pfeffer et al[46]	DB, MC, RCT	N=14,703	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
VALIANT Captopril 50 mg TID vs valsartan 160 mg BID vs combination valsartan 80 mg BID and captopril 50 mg TID	Men and women ≥18 years with an acute myocardial infarction that was complicated by clinical or radiologic signs of heart failure and/or evidence of left ventricular systolic dysfunction	24.7 months	All-cause mortality Secondary: Death from cardiovascular causes, recurrent MI, hospitalization for heart failure	No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (*P*=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (*P*=0.73). Secondary: The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (*P*=0.20). The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (*P*=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash, and taste disturbance were more common in the captopril group.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, HCTZ=hydrochlorothiazide, Q AM=every morning, QD=once daily, SR=sustained-release, TID=three times daily
Study abbreviations: AC=active comparator, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, XO=cross over
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, CAD=coronary artery disease, DBP=diastolic blood pressure, ESRD=end-stage renal disease, HDL-C=high-density lipoprotein cholesterol, JNC=Joint National Committee, LDL-C=low-density lipoprotein cholesterol, PVD=peripheral vascular disease, SBP=systolic blood pressure, TC=total cholesterol, TIA=transient ischemic attack

Additional Evidence

Dose Simplification
Taylor et al[47] compared the compliance rate of patients on a fixed-dose combination of amlodipine and benazepril to patients receiving an angiotensin-converting enzyme (ACE) inhibitor and a long-acting dihydropyridine calcium-channel blocking agent as separate pills. Medication adherence was calculated by the medication possession ratio (MPR), defined as the total day supply of medication divided by the number of days between prescription fillings. Group 1 consisted of 2,754 patients receiving the fixed-dose amlodipine and benazepril combination and group 2 included 2,978 patients taking an ACE inhibitor and a dihydropyridine as separate agents. There was no significant difference in adherence in younger subjects (18-39 year olds); however, overall adherence (MPR) through all ages was higher in group 1 (combination amlodipine and benazepril) compared to group 2 (80.8% vs 73.8%; $P<0.001$). It should be noted that a significantly higher number of subjects in group 2 had additional comorbidities, including diabetes, heart failure and coronary artery disease. The differences in MPRs are equivalent to being compliant 26 more days per year with the combination agent. Dickson and Plauschinat also evaluated compliance rates with fixed-dose combination of amlodipine and benazepril versus administration of an ACE inhibitor and dihydropyridine calcium channel antagonist prescribed as separate agents (free-combination) in an elderly Medicaid population.[48] Over a 12 month period, compliance rates as determined by prescription claims were reported to be significantly higher with fixed-dose versus free-combination therapy (63.4% vs 49.0%; $P<0.0001$). This study had several limitations. It was funded by the manufacturer of the combination product, including one author who was an employee of that company. In addition, it was a non-randomized, retrospective study based on historical claims which did not control for once daily dosing in the comparator group, nor did it include any clinical outcomes.

Dezzi also reported significantly higher compliance rates at 12 months in patients receiving fixed-dose lisinopril and hydrochlorothiazide (68.7%) or enalapril and hydrochlorothiazide (70.0%) versus administration of the separate components (57.8% and 57.5%, respectively; $P<0.05$ for both comparisons).[49] All 3 of these studies were performed by evaluating pharmacy claims and the impact of increased compliance on improved clinical outcomes was not evaluated and/or reported.

Stable Therapy
Sapienza et al[50] measured the impact of converting 51 long-term care patients previously on high dose calcium-channel blocking agents or dual therapy with an ACE inhibitor and calcium-channel blocking agents to combination amlodipine and benazepril. There was no significant change in blood pressure from baseline following the conversion; however, there was a significant reduction (81.8%) in the number of patients reporting ≥1 drug-related adverse event (22 vs 4; $P<0.05$), particularly edema (75% reduction).

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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

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

Rx=prescription.

Table 11. Relative Cost of the Combination Angiotensin-Converting Enzyme Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
benazepril and amlodipine	capsule	Lotrel®*	$$$$	$$$
benazepril and hydrochlorothiazide	tablet	Lotensin HCT®*	$$	$
captopril and hydrochlorothiazide	tablet	Capozide®*	$$	$
enalapril and felodipine	sustained-release tablet	Lexxel®	$$$	N/A
enalapril and hydrochlorothiazide	tablet	Vaseretic®*	$$$	$$
fosinopril and hydrochlorothiazide	tablet	Monopril HCT®*	$$	$$
lisinopril and hydrochlorothiazide	tablet	Prinzide®*, Zestoretic®*	$$	$
moexipril and hydrochlorothiazide	tablet	Uniretic®*	$$	$$
quinapril and hydrochlorothiazide	tablet	Accuretic®*	$$	$$
trandolapril and verapamil	extended-release tablet	Tarka®	$$$	N/A

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

X. Conclusions

The combination angiotensin-converting enzyme (ACE) inhibitors contain an ACE inhibitor in a fixed-dose combination with a thiazide diuretic (hydrochlorothiazide) or calcium-channel blocking agent (amlodipine, felodipine or verapamil). All of the combination ACE inhibitors that contain hydrochlorothiazide and amlodipine are available generically. In addition, all of the individual components of the combination ACE inhibitors are available generically. All of the combination ACE inhibitors are Food and Drug Administration (FDA) approved for the treatment of hypertension. Only the fixed-dose combination product containing captopril and hydrochlorothiazide is approved for initial treatment of hypertension.

The consensus guidelines recognize that many patients will require more than one medication to control blood pressure.[5-12] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) states that most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes and recommends that thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy.[5] ACE inhibitors and calcium-channel blocking agents are recommended as first-line agents in patients with hypertension and other comorbid conditions. Combination ACE inhibitors are intended to maximize the antihypertensive effect of each individual agent and minimize the potential for dose-related adverse effects.

The clinical trials summarized in the effectiveness section demonstrated that combination therapy, either administered as a fixed-dose combination product or separate components, significantly lowered blood pressure compared to monotherapy with either agent with comparable or fewer adverse events. In addition, more patients who were inadequately controlled on monotherapy achieved blood pressure goals while on combination therapy. Several studies reported that combination products were safe and effective for the initial treatment of hypertension. While several retrospective analyses have reported improved compliance with the fixed-dose combination products, there is insufficient evidence to conclude that combination products are significantly more effective than administration of the separate components.[47-50]

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand combination angiotensin-converting enzyme inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Angiotensin II Receptor Antagonists
Single Entity Agents
AHFS Class 243208
September 10, 2008

I. Overview

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[1,2] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[3] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[1,3] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy and remodeling.[1,2] The RAAS plays an important role in the development and progression of heart failure.[2]

The ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator associated with dry cough.[1-4] Since angiotensin II may also be generated through other pathways that do not depend upon ACE (eg, chymase), blockade of angiotensin II by ACE inhibitors is incomplete.[1,2] Angiotensin II receptor antagonists or blockers (ARBs) block the angiotensin II receptor subtype AT_1, preventing the negative effects of angiotensin II, regardless of its origin. ARBs do not appear to affect bradykinin. Evidence-based guidelines recognize the important role that ACE inhibitors and ARBs play in the treatment of various cardiovascular and associated complications, such as renal disease.

The single entity ARBs that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products within this class.

Table 1. Single Entity Angiotensin II Receptor Antagonists Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
candesartan	tablet	Atacand®	none
eprosartan	tablet	Teveten®	none
irbesartan	tablet	Avapro®	Avapro®
losartan	tablet	Cozaar®	Cozaar®
olmesartan	tablet	Benicar®	Benicar®
telmisartan	tablet	Micardis®	Micardis®
valsartan	tablet	Diovan®	Diovan®

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines using the single entity angiotensin II receptor antagonists (ARBs) are summarized in Table 2. For a more comprehensive overview of the pharmacologic treatment of angina pectoris, chronic heart failure, hypertension, and acute myocardial infarction, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Single Entity Angiotensin II Receptor Antagonists

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/American Heart Association (AHA):	• Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin-converting enzyme inhibitors (ACE inhibitors) and/or β-adrenergic blocking agents (β-blockers) with the addition of other medications as needed to achieve blood pressure

Clinical Guideline	Recommendation
2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)[5]	goals of <140/90 mm Hg or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction of ≤40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal left ventricular ejection fraction in whom cardiovascular risk factors remain well controlled and revascularization has been performed) unless contraindicated. • ARBs are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction and have a left ventricular ejection fraction of ≤40%. • ARBs may be considered in combination with an ACE inhibitor due to left ventricular systolic dysfunction.
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)[6]**	• Inhibitors of the renin-angiotensin-aldosterone system can be used in the acute setting during early hospitalization. • ACE inhibitors should be initiated and continued indefinitely in patients with heart failure, left ventricular dysfunction, diabetes, or hypertension unless contraindicated. ARBs should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and signs of heart failure and left ventricular ejection fraction <40%. • ACE inhibitors are reasonable for all patients, even without left ventricular dysfunction, hypertension, or diabetes mellitus unless contraindicated. • ACE inhibitors are reasonable for patients with heart failure and left ventricular ejection fraction <40%. • Patients who cannot tolerate ACE inhibitors may be treated with an ARB if they have signs of heart failure and left ventricular ejection fraction <40%. • Combination ACE inhibitor and ARB therapy may be considered in patients with persistent symptomatic heart failure and left ventricular ejection fraction <40% despite conventional therapy including an ACE inhibitor or ARB alone, unless the patient is already on an aldosterone antagonist. • In patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with chronic kidney disease or diabetes mellitus), it is useful to add blood pressure medication(s) as tolerated, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve target blood pressure.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)[7]**	<u>Therapy to Improve Prognosis</u> • ACE inhibitors should be considered in patients with stable angina and comorbid hypertension, diabetes, heart failure, asymptomatic left ventricular dysfunction, and patients who have had a myocardial infarction. Patients with stable angina who do not have an indication for an ACE inhibitor may be treated with one if the benefits of the agent (possible absolute risk reduction) outweigh the possible side effects. • The role of ARBs is not addressed in this guideline. <u>Treatment of Syndrome X</u> • ACE inhibitors are recommended in patients with hypertension. • The role of ARBs is not addressed in this guideline.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS) (2007)[8]**	• ACE inhibitors are recommended in all patients with left ventricular ejection fraction ≤40% and in patients with diabetes, chronic kidney disease, and hypertension unless otherwise contraindicated. • ACE inhibitors should be considered for all other patients to prevent the recurrence of ischemia. Agents and doses of proven efficacy are recommended (ramipril and perindopril). • ARBs should be considered in patients intolerant to ACE inhibitors and/or who have

Clinical Guideline	Recommendation
	heart failure or have had a myocardial infarction with a left ventricular ejection fraction of ≤40%.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease (2004)**[9]	Symptomatic Patients • The following agents are recommended to prevent myocardial infarction or death and to reduce symptoms: aspirin (clopidogrel may be used in patients intolerant to aspirin), β-blockers, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), and ACE inhibitors. • The role of ARBs was not addressed in this guideline. Asymptomatic Patients With Evidence Suggesting CAD on Previous Testing • The following agents should be used to prevent myocardial infarction and death: aspirin (in patients with a previous myocardial infarction), β-blockers (in patients with a previous myocardial infarction), statins (in patients with type 2 diabetes or documented CAD), and an ACE inhibitor (in patients with documented CAD and diabetes, systolic dysfunction, or both). • The following agents may also be used to prevent myocardial infarction and death: aspirin in patients who have not had a previous myocardial infarction, and an ACE inhibitor in patients with diabetes and no contraindications. • The role of ARBs was not addressed in this guideline.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[10]	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors, and β-blockers have been shown to prevent heart failure. The ARBs losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes mellitus and nephropathy. • Lipid disorders should be treated according to contemporary guidelines. • ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, myocardial infarction, and heart failure. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left ventricular dysfunction or hypertension. • ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes, and hypertension with other cardiovascular risk factors. Patients With Cardiac Structural Abnormalities or Remodeling Who Have not Developed Heart Failure Symptoms (Stage B) • β-Blockers and ACE inhibitors should be used in all patients with a recent or past history of myocardial infarction. • β-Blockers and ACE inhibitors should be used in patients who have reduced left ventricular ejection fraction and do not have a history of myocardial infarction or heart failure. • ARBs are recommended for patients with reduced left ventricular ejection fraction and a history of a myocardial infarction if they are intolerant to ACE inhibitors. • ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • ACE inhibitors are recommended in all patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated. • ARBs approved for the treatment of heart failure are recommended in all patients intolerant to ACE inhibitors with current or past symptoms of heart failure and reduced left ventricular ejection fraction.

Clinical Guideline	Recommendation
	• ARBs are reasonable alternatives to ACE inhibitors as first-line therapy in patients with mild-to-moderate heart failure and reduced left ventricular ejection fraction. • The addition of an ARB is reasonable in patients who are symptomatic despite conventional treatment. • The routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended. <u>Patients With Heart Failure and Normal Left Ventricular Ejection Fraction</u> • β-Blockers, ARBs, ACE inhibitors, and calcium-channel blocking agents (CCBs) may be useful in patients with heart failure and controlled hypertension to improve symptoms.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[11]	<u>Patients at Risk for Development of Heart Failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction</u> • ACE inhibitors are recommended. ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of ACE inhibitors and ARBs together is not recommended. <u>Patients With Left Ventricular Systolic Dysfunction</u> • ACE inhibitors should be used in all patients with a left ventricular ejection fraction ≤40% unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a left ventricular ejection fraction ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a myocardial infarction and have left ventricular dysfunction is not recommended. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a myocardial infarction and in patients with chronic heart failure and systolic dysfunction. <u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least 1 other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. <u>Patients With Heart Failure and Coronary Artery Disease</u> • ACE inhibitors are recommended after a myocardial infarction. • ACE inhibitor and β-blocker therapy should be initiated early (within 48 hours) in hospitalized stable patients who have had a myocardial infarction and have left ventricular dysfunction. <u>Managing Patients With Heart Failure and Hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or CCB.

Clinical Guideline	Recommendation
	• Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent. • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing CCB (amlodipine) may be considered. <u>Managing Heart Failure in the Elderly, Women, and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)**[12]	• ACE inhibitors are recommended in patients with left ventricular ejection fraction 40% to 45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention. • ARBs may be used in patients who are intolerant to ACE inhibitor therapy. They may also be used in combination with ACE inhibitors in patients who remain symptomatic. • High doses of ARBs may reduce hospitalizations in patients with heart failure and preserved left ventricular ejection fraction or diastolic dysfunction.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)**[13]	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • In patients with acute coronary syndromes (myocardial infarction or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. • For patients with post-myocardial infarction, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE

Clinical Guideline	Recommendation
	inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2 to 4 times higher in African American patients. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant. • ACE inhibitors should not be used in patients who have a history of angioedema.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[14]	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics, dihydropyridine CCBs), renal disease (ACE inhibitors, ARBs), post-myocardial infarction (ACE inhibitors, β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics, ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[15]	• The choice of drug should depend on several factors, including previous patient response to a class of medications, the effect of a medication on cardiovascular risk according to the patient's cardiovascular profile, presence of compelling indications for certain medications, the presence of disorders which may limit the use of a class of medications, possibility of drug interactions, and side effects. • Drugs which exert their effects for 24 hours and can be given once daily should be preferred to enhance compliance. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors, ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end-stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[16]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • Initial therapy in patients younger than 55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added.

Clinical Guideline	Recommendation
Primary Care: Pharmacological Update (2006)[17]	
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008[18]**	General Recommendations • If ACE inhibitors, ARBs or diuretics are used, kidney function and serum potassium levels should be closely monitored. • ACE inhibitors and ARBs are contraindicated during pregnancy. Hypertension • Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2. Coronary Heart Disease • In patients with known cardiovascular disease and in patients >40 years with another cardiovascular risk factor, ACE inhibitor, aspirin, and statin therapy (if not contraindicated) should be used to reduce the risk of cardiovascular events. Diabetic Nephropathy • In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used. • While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements: • In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. • In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. • In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy. • If one class is not tolerated, the other should be substituted.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)[19]**	• All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy. • CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • African American patients appear to be at an increased risk for ACE inhibitor-associated cough, angioedema, or both. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI):	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling

Clinical Guideline	Recommendation
K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)[20]	indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-myocardial infarction with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-myocardial infarction (β-blockers), chronic stable angina (CCBs, β-blockers), high CAD risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), and supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)**[21]	Secondary Prevention • Patients with comorbid hypertension should be treated initially with β-blockers and/or ACE inhibitors with the addition of other medications as needed to achieve a blood pressure goal of <140/90 mm Hg (or <130/80 mm Hg in patients with diabetes or chronic kidney disease). • ACE inhibitors are recommended in all patients with a left ventricular ejection fraction ≤40% and those with hypertension, diabetes, or chronic kidney disease unless contraindicated. • ACE inhibitors are reasonable in patients with normal left ventricular function and well-controlled cardiovascular risk factors. • ARBs are recommended in patients who are intolerant to ACE inhibitors and have heart failure or who have a left ventricular ejection fraction of ≤40%. • ARBs should be considered in all patients intolerant to ACE inhibitor therapy. • Combination therapy with ARBs and ACE inhibitors may be considered in patients with systolic dysfunction heart failure.
National Institute for Health and Clinical Excellence (NICE): **Post-Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)**[22]	• An ACE inhibitor is recommended for all patients who have had a myocardial infarction. • ACE inhibitors are recommended early after presentation with an acute myocardial infarction. • ARBs are recommended in patients who are intolerant to ACE inhibitor therapy. • Combination therapy with an ACE inhibitor and an ARB is not routinely recommended. • In patients with a proven myocardial infarction in the past and with heart failure and left ventricular systolic failure, treatment should be in line with recommendations for chronic heart failure. • In patients with a proven myocardial infarction in the past and with asymptomatic left ventricular systolic dysfunction and in those without heart failure and preserved left ventricular function, ACE inhibitors are recommended (ARBs may be given to patients who are intolerant of ACE inhibitors).
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)**[23]	Prophylactic Therapies in the Acute Phase • ACE inhibitor should be initiated within 24 hours. • The role of ARBs was not addressed in this guideline. Secondary Prevention • ACE inhibitors should be continued unless contraindicated. • The role of ARBs was not addressed in this guideline.

III. Indications

Food and Drug Administration (FDA)-approved indications for the single entity angiotensin II receptor antagonists 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 Single Entity Angiotensin II Receptor Antagonists[24-30]

Drug	Diabetic Nephropathy	Heart Failure (New York Heart Association Classes II-IV)	Hypertension	Hypertension With Left Ventricular Hypertrophy	Post-Myocardial Infarction
Candesartan		✔ *	✔		
Eprosartan			✔		
Irbesartan	✔ (type 2 diabetes and hypertension)		✔		
Losartan	✔ (type 2 diabetes and history of hypertension)		✔	✔ (to reduce risk of stroke)†	
Olmesartan			✔		
Telmisartan			✔		
Valsartan		✔ ‡	✔		✔ (to reduce cardiovascular mortality)§

*Atacand® is indicated for the treatment of heart failure in patients with left ventricular systolic dysfunction (ejection fraction ≤40%) to reduce cardiovascular death and to reduce heart failure hospitalizations. Atacand® also has an added effect on these outcomes when used with an Angiotensin Converting Enzyme (ACE) inhibitor.
†There is evidence that this benefit does not apply to African American patients.
‡In a controlled clinical trial, Diovan® significantly reduced hospitalizations for heart failure. There is no evidence that Diovan® provides added benefits when it is used with an adequate dose of an ACE inhibitor.
§Diovan® is indicated to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity angiotensin II receptor antagonists are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Single Entity Angiotensin II Receptor Antagonists[31,32]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Candesartan	~15	>99	CYP2C9	Yes; CV-11974	Feces (~67); renal (~33)	~9
Eprosartan	~13	~98	Glucuronidation	No	Feces (~90); renal (~7)	5-9
Irbesartan	60-80	90	CYP2C9	No	Feces (65); renal (20)	11-15
Losartan	25-35	99	CYP2C9; CYP3A4	Yes; 5-carboxylic acid (E-3174)	Feces (50-60); renal (13-35)	~2 (6-9)*
Olmesartan	~26	99	Deesterification	Yes; RNH-6270 (deesterified olmesartan)	Feces (50-65); renal (35-50)	~13
Telmisartan	42-58	>99.5	Conjugation	No	Feces (>97)	~24

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Valsartan	~25	95	Minimal	No	Feces (~83); renal (~7-13)	~6-9

*Metabolite.

V. Drug Interactions

Significant drug interactions with the single entity angiotensin II receptor antagonists are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Single Entity Angiotensin II Receptor Antagonists[31]

Drug(s)	Significance Level	Interaction	Mechanism
Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan	1	Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	Angiotensin II receptor antagonists and potassium-sparing diuretics may increase serum potassium levels, leading to additive or synergistic effects.
Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan	2	Lithium	Angiotensin II receptor antagonists may decrease lithium renal excretion by enhancing its reabsorption. Lithium levels may increase, resulting in an increase in pharmacologic and toxic effects of lithium.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the single entity angiotensin II receptor antagonists are noted in Table 6. The black box warning regarding the use of these agents during pregnancy is summarized in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Single Entity Angiotensin II Receptor Antagonists[31]

Adverse Event	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Central Nervous System							
Anxiety/ nervousness	≥0.5	<1	≥1	<1	-	>0.3	>0.2
Depression	≥0.5	1	<1	<1	-	>0.3	-
Dizziness	4	≥1	≥1	3.5	3	1	>1
Fatigue	>1	2	4	-	>0.5	1	2
Headache	≥1	≥1	≥1	≥1	>1	1	>1
Insomnia	-	<1	-	1.4	>0.5	>0.3	>0.2
Gastrointestinal							
Abdominal pain	>1	2	≥1	≥1	>0.5	1	2
Diarrhea	>1	≥1	3	2.4	>1	3	>1
Dyspepsia/ heartburn	≥0.5	≥1	2	1.3	>0.5	1	>0.2
Nausea/vomiting	>1	<1	≥1	≥1	-	1	>1
Musculoskeletal							
Arthralgia	>1	2	-	<1	>0.5	>0.3	>1
Muscle cramp	-	-	-	1.1	-	-	>0.2
Myalgia	≥0.5	≥1	-	1	>0.5	1	>0.2
Pain (includes back and leg)	3	<1	≥1	1-1.8	>1	1-3	>0.2
Trauma	-	-	2	-	-	-	-
Respiratory							
Bronchitis	>1	≥1	-	<1	>1	>0.3	-

Adverse Event	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Cough	>1	4	2.8	3.4	-	1	>1
Influenza/ influenza-like symptoms	-	<1	≥1	<1	>1	1	-
Nasal congestion	-	-	-	2	-	-	-
Pharyngitis	2	4	≥1	≥1	>1	1	>1
Rhinitis	2	4	≥1	<1	>1	>0.3	>1
Sinus disorder	-	-	≥1	1.5	-	-	-
Sinusitis	>1	≥1	-	1	>1	3	>1
Upper respiratory tract infection	6	8	9	7.9	>1	7	>1
Miscellaneous							
Albuminuria	>1	<1	-	-	-	-	-
Angioedema	✔	✔	✔	✔	✔	✔	✔
Chest pain	>1	≥1	≥1	≥1	>0.5	1	-
Edema	-	≥1	≥1	≥1	-	-	>1
Elevated creatine phosphokinase	≥0.5	<1	-	-	>1	-	-
Hematuria	≥0.5	<1	-	-	>1	-	-
Hyperglycemia	≥0.5	<1	-	-	>1	-	-
Hyperkalemia	✔	<1	rare	✔	-	-	✔
Hypertension	-	-	<1	-	-	-	-
Hyper-triglyceridemia	≥ 0.5	1	-	-	>1	-	-
Hypotension	-	<1	0.4	<1	-	-	<1
Inflicted injury	-	2	-	-	>1	-	-
Peripheral edema	>1	-	-	-	>0.5	1	-
Rash	≥0.5	<1	≥1	<1	>0.5	>0.3	>0.2
Tachycardia	≥0.5	<1	≥1	<1	>0.5	>0.3	-
Urinary tract infection	-	4	≥1	<1	>0.5	1	-
Viral infection	-	2	-	-	-	-	3

- Event not reported or incidence <1%.
✔ Percent not specified.

Table 7. Black Box Warning for the Single Entity Angiotensin II Receptor Antagonists[24-30]

WARNING: USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, the angiotensin II receptor antagonist should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

VII. Dosing and Administration

The usual dosing regimens for the single entity angiotensin II receptor antagonists are summarized in Table 8. Losartan and valsartan are Food and Drug Administration (FDA) approved for the treatment of hypertension in pediatric patients who are 6 years of age and older.

Table 8. Usual Dosing for the Single Entity Angiotensin II Receptor Antagonists[24-30]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Candesartan	Heart failure: Initial: 4 mg once daily; target: 32 mg once daily	Safety and efficacy in children have not been established.	Tablet: 4 mg 8 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertension: Initial: 16 mg once daily when used as monotherapy in patients who are not volume-depleted; maintenance: 8 to 32 mg per day in 1 or 2 divided doses		16 mg 32 mg
Eprosartan	Hypertension: Initial: 600 mg once daily when used as monotherapy in patients who are not volume-depleted; maintenance: 400 to 800 mg per day in 1 or 2 divided doses	Safety and efficacy in children have not been established.	Tablet: 400 mg 600 mg
Irbesartan	Diabetic nephropathy: Target: 300 mg once daily Hypertension: Initial: 150 mg once daily in patients who are not volume-depleted; maximum: 300 mg once daily	Hypertension: In a study at a dose of up to 4.5 mg/kg/day once daily, irbesartan did not appear to lower blood pressure effectively in pediatric patients aged 6 to 16 years. Irbesartan has not been studied in pediatric patients <6 years of age.	Tablet: 75 mg 150 mg 300 mg
Losartan	Diabetic nephropathy: Initial: 50 mg once daily; dose should be increased to 100 mg once daily based on blood pressure response Hypertension: Initial: 50 mg once daily in patients who are not volume-depleted; maintenance: 25 to 100 mg per day in 1 or 2 divided doses Left ventricular hypertrophy in hypertensive patients: Initial: 50 mg once daily; hydrochlorothiazide 12.5 mg daily should be added and/or the losartan dose increased to 100 mg once daily followed by an increase in hydrochlorothiazide 25 mg once daily based on blood pressure response	Hypertension in pediatric patients 6 years of age and older: Initial: 0.7 mg/kg once daily (up to 50 mg total) administered as a tablet or suspension; doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied (See package insert for compounding procedures for suspension.)	Tablet: 25 mg 50 mg 100 mg
Olmesartan	Hypertension: Initial: 20 mg once daily when used as monotherapy in patients who are not volume depleted; maximum: 40 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 20 mg 40 mg
Telmisartan	Hypertension: Initial: 40 mg once daily; maximum: 80 mg per day	Safety and efficacy in children have not been established.	Tablet: 20 mg 40 mg 80 mg
Valsartan	Heart failure: Initial: 40 mg twice daily; uptitration to 80 to 160 mg twice daily should be done to the highest dose as tolerated; maximum: 320 mg in divided doses Hypertension:	Hypertension in pediatric patients 6 to 16 years of age: Initial: 1.3 mg/kg once daily (up to 40 mg total) administered as a tablet or suspension; doses above	Tablet: 40 mg 80 mg 160 mg 320 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Initial: 80 to 160 mg once daily when used as monotherapy in patients who are not volume depleted; maintenance: 80 to 320 mg once daily Post-myocardial infarction: Initial: 20 mg twice daily; target: 160 mg twice daily	2.7 mg/kg (or in excess of 160 mg) daily have not been studied; exposure to valsartan with the suspension is 1.6 times greater than with the tablet (See package insert for compounding procedures for suspension.)	

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity angiotensin II receptor antagonists are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Single Entity Angiotensin II Receptor Antagonists

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypertension				
Lithell et al[33] SCOPE Candesartan 16 mg/day vs placebo in addition to conventional therapy (diuretics, ACE inhibitors, β-blockers, calcium-channel blocking agents)	DB, MC, PC, PG, RCT Patients 70-89 years old with mild-to-moderate hypertension (SBP 160-179 mm Hg and/or DBP 90-99 mm Hg) and MMSE scores ≥24	N=4,964 3.7 years	Primary: First major coronary event including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke Secondary: cardiovascular death, nonfatal and fatal stroke and myocardial infarction, cognitive function	Primary: Results showed no significant difference in the primary end point between candesartan and placebo (*P*=0.19). Secondary: Candesartan treatment reduced nonfatal stroke by 27.8% (*P*=0.04) and all stroke by 23.6% (*P*=0.056) compared to placebo. There were no significant differences in myocardial infarction and cardiovascular mortality. Mean MMSE score fell from 28.5 to 28.0 in the candesartan group and from 28.5 to 27.9 in the control group (*P*=0.20). The proportion of patients who had a significant cognitive decline or developed dementia was not different in the 2 groups.
Baguet et al[34] Candesartan 8 mg QD (n=87) vs losartan 50 mg QD (n=89) vs placebo (n=80)	DB, RCT Patients with mild-to-moderate essential hypertension (DBP 95-115 mm Hg)	N=256 6 weeks	Primary: Change in mean ambulatory DBP from baseline to the 0-24 hour period after the last dose of study medication Secondary: Change in mean ambulatory SBP from baseline to the 0-24 hour period after the last dose of study medication, change in DBP and SBP during	Primary: At the end of the 6 weeks, the mean change in DBP between the baseline and the 0-24 hour period after the last dose of study medication was greater in patients receiving candesartan 8 mg compared with losartan (–7.3 vs –5.1 mm Hg; *P*<0.05) or placebo (0.3 mm Hg; *P*<0.001). Secondary: The mean change in SBP between the baseline and the 0-24 hour period after the last dose of study medication was greater in patients receiving candesartan (–10.8 mm Hg) or losartan (–8.8 mm Hg) than placebo (1.2 mm Hg; *P*<0.001). Candesartan was associated with a greater reduction in DBP and SBP relative to placebo, when compared with losartan during both the daytime and nighttime, and between 12 and 24 hours after dosing

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			the daytime and nighttime, change in DBP and SBP between 12 and 24 hours after dosing	(*P*<0.001). Both active treatments were well tolerated.
Robles et al[35] ESTEPP Eprosartan 600 mg QD	MC, OL, PRO Patients with mild-to-moderate hypertension with and without diabetes, mean age 65 years for patients with diabetes and 63 years for patients without diabetes	N=549 (n=114 diabetics and n=435 nondiabetics) 16 weeks	Primary: Changes in blood pressure, compliance, adverse effects Secondary: Not reported	Primary: Blood pressure decreased significantly (*P*<0.0001) in both diabetic and nondiabetic patients (SBP 25.9 vs 26.0 mm Hg), DBP (12.5 vs 13.2 mm Hg), MAP (16.9 vs 17.5 mm Hg) and pulse pressure (13.4 vs 12.8 mm Hg). Pulse pressure/MAP ratio showed a significant reduction in diabetics and nondiabetics. Treatment compliance did not differ between the groups (diabetics 98.0% vs nondiabetics 92.2%). The adverse effect rate was 7% in diabetic patients and 2.8% in nondiabetics. Secondary: Not reported
Dahlöf et al[36] LIFE Losartan 50 to 100 mg/day with HCTZ 12.5 to 25 mg/day if needed for blood pressure control vs atenolol 50 to 100 mg/day, with HCTZ 12.5 to 25 mg/day if needed for blood pressure control	DB, DD, PG, RCT Patients 55 to 80 years old with essential hypertension (sitting SBP/DBP 160-200/95-115 mm Hg) and LVH	N=9,193 ≥4 years	Primary: Composite of cardiovascular death, myocardial infarction and stroke Secondary: All-cause mortality, hospitalization for angina or heart failure, revascularization procedures, resuscitated cardiac arrest, new-onset diabetes	Primary: SBP fell by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively (treatment difference, *P*=0.017) and DBP fell by 16.6 and 16.8 mm Hg, respectively (treatment difference, *P*=0.37). MAP was 102.2 and 102.4 mm Hg, respectively (*P*=NS). Heart rate decreased more in patients assigned to atenolol than losartan (–7.7 vs –1.8 beats/minute, respectively; *P*<0.0001). Compared to atenolol, the primary composite occurred in 13.0% fewer patients receiving losartan (RR, 0.87; 95% CI, 0.77 to 0.98; *P*=0.021). While there was no difference in the incidence cardiovascular mortality (*P*=0.206) and myocardial infarction (*P*=0.491), losartan treatment resulted in a 24.9% relative risk reduction in stroke compared to atenolol (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: A 25% lower incidence of new-onset diabetes was reported with losartan compared to atenolol (*P*=0.001). There was no significant difference among the other secondary end points between the 2 treatment groups. Note: At end point or end of follow-up, 18% and 26% of patients on losartan were receiving HCTZ alone or with other drugs, respectively. In the atenolol group, 16% and 22% of patients were receiving HCTZ alone or with other drugs, respectively.
Julius, Alderman et al[37] LIFE Black Subset Losartan 50 to 100 mg/day with HCTZ 12.5 to 25 mg/day if needed for blood pressure control vs atenolol 50 to 100 mg/day, with HCTZ 12.5 to 25 mg/day if needed for blood pressure control	Post hoc analysis Patients 55 to 80 years old with essential hypertension (sitting SBP/DBP 160-200/95-115 mm Hg) and LVH	N=523 ≥4 years	Primary: Composite of cardiovascular death, myocardial infarction and stroke Secondary: Not reported	Primary: Compared with atenolol (11.2%), losartan in the United States African American population resulted in a greater incidence of the composite end point (17.4%; *P*=0.033). Hazard ratios favored atenolol across all parameters (*P*=0.246 for cardiovascular mortality, *P*=0.140 for myocardial infarction, and *P*=0.030 for stroke). In African American patients, blood pressure reduction was similar in both groups, and regression of electrocardiographic-LVH was greater with losartan. Secondary: Not reported
Lindholm et al[38] LIFE Diabetic Subset Losartan 50 to 100 mg/day with HCTZ 12.5 to 25 mg/day if needed for blood pressure control	Post hoc analysis Patients 55 to 80 years old with essential hypertension (sitting SBP/DBP 160-200/95-115 mm Hg) and LVH	N=1,195 ≥4 years	Primary: Composite of cardiovascular death, myocardial infarction and stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a 24% decrease in the primary composite end point (*P*=0.031). Losartan treatment resulted in a 37% risk reduction in cardiovascular deaths vs atenolol (*P*=0.028). Losartan treatment resulted in a 39% risk reduction in all-cause mortality vs atenolol (*P*=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atenolol 50 to 100 mg/day, with HCTZ 12.5 to 25 mg/day if needed for blood pressure control				Mean blood pressure fell to 146/79 mm Hg in losartan patients and 148/79 mm Hg in atenolol patients. Secondary: Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively (RR, 0.61; *P*=0.002).
Kjeldsen et al[39] LIFE Isolated Systolic Hypertension Subset Losartan 50 to 100 mg/day with HCTZ 12.5 to 25 mg/day if needed for blood pressure control vs atenolol 50 to 100 mg/day, with HCTZ 12.5 to 25 mg/day if needed for blood pressure control	Post hoc analysis Patients 55 to 80 years old with isolated systolic hypertension (SBP of 160-200 mm Hg and DBP <90 mm Hg) and LVH	N=1,326 ≥4 years	Primary: Composite of cardiovascular death, myocardial infarction, or stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a trend towards a 25% reduction in the primary end point (*P*=0.06). Losartan treatment resulted in a 46% risk reduction in cardiovascular mortality (*P*=0.01) and 40% risk reduction in stroke compared to atenolol (*P*=0.02). There was no difference in the incidence of myocardial infarction. Blood pressure was reduced by 28/9 and 28/9 mm Hg in the losartan and atenolol arms. Secondary: Patients receiving losartan also had reductions in all-cause mortality (28%; *P*<0.046).
Oparil et al[40] Olmesartan 20 mg/day vs irbesartan 150 mg/day, losartan 50 mg/day or valsartan 80 mg/day	DB, MC, PG, RCT Patients ≥18 years old (mean age 52 years) with essential hypertension (cuff DBP ≥100 mm Hg and ≤115 mm Hg and mean daytime DBP ≥90 mm Hg and <120 mm Hg)	N=588 8 weeks	Primary: Change in seated cuff DBP at week 8 compared to olmesartan Secondary: Change in seated cuff SBP at week 8, 24-hour DBP and SBP, adverse events	Primary: The mean reductions in seated cuff DBP at week 8 were significantly greater with olmesartan (11.5 mm Hg) than with irbesartan (9.9 mm Hg; *P*=0.0412), losartan (8.2 mm Hg; *P*=0.0002) and valsartan (7.9 mm Hg; *P*<0.0001). The clinical significance of a few mm Hg DBP difference between the groups is unknown. Secondary: Reductions of cuff SBP were not significantly different among the 4 ARBs and ranged from 8.4 to 11.3 mm Hg.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The reduction in mean 24-hour DBP with olmesartan (8.5 mm Hg) was significantly greater than reductions with losartan and valsartan (6.2 and 5.6 mm Hg, respectively) and showed a trend toward significance when compared to irbesartan (7.4 mm Hg; *P*=0.087). The reduction in mean 24-hour SBP with olmesartan (12.5 mm Hg) was significantly greater than the reductions with losartan and valsartan (9.0 and 8.1 mm Hg, respectively) and equivalent to the reduction with irbesartan (11.3 mm Hg). All drugs were well tolerated with the incidence of adverse events reported in 30.6% of patients in the olmesartan group, 35.6% for irbesartan, 32.0% for losartan, and 44.8% for valsartan.
Brunner et al[41] Olmesartan 20 mg QD vs candesartan 8 mg QD	DB, RCT Patients with mainly mild-to-moderate hypertension	N=635 8 weeks	Primary: 24-hour antihypertensive efficacy (with particular emphasis on blood pressure control during the early morning period), proportion of patients who achieved various ABPM goals (SBP/DBP <125/80 mm Hg) Secondary: Not reported	Primary: After 8 weeks, significantly greater proportions of patients treated with olmesartan achieved 24-hour and daytime ABPM goals 25.6% and 18.3%, respectively) compared with candesartan (14.9%; *P*<0.001 and 9.6%; *P*=0.002, respectively). During the last 4 hours of 24-hour ABPM, the proportion of patients who achieved goals was significantly greater with olmesartan (33.3%) than candesartan (22.9%; *P*<0.001). Similarly, during the last 2 hours of 24-hour ABPM, the proportion of patients who achieved these blood pressure goals was higher with olmesartan (26.9% and 19.9%) compared to candesartan (19.6%; *P*=0.028 and 14.3%; *P*=0.061). Secondary: Not reported
Xi et al[42] Telmisartan vs	MA of 11 RCT Patients with hypertension	N=1,832 Duration varied	Primary: Reduction in DBP and SBP Secondary: Therapeutic response	Primary: Use of telmisartan resulted in a significant reduction in clinic DBP (WMD, 1.52; 95% CI, 0.85 to 2.19) and SBP (WMD, 2.77; 95% CI, 1.90 to 3.63) when compared with losartan. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
losartan			of DBP and SBP, tolerability	There was also a significant reduction in 24-hour mean ambulatory DBP (WMD, 2.49; 95% CI, 0.56 to 4.42) and SBP (WMD, 2.47; 95% CI, 0.40 to 4.55) with telmisartan as compared to losartan. There was a significant increase in therapeutic response of DBP (RR, 1.14; 95% CI, 1.04 to 1.23) and SBP response (RR, 1.10; 95% CI, 1.01 to 1.20) with telmisartan as compared to losartan. Both telmisartan and losartan were well tolerated.
Julius, Kjeldsen et al[43] VALUE Valsartan 80 to 160 mg/day vs amlodipine 5 to 10 mg/day	DB, PG, RCT Patients ≥50 years old with treated or untreated hypertension and history of CVD, stroke, or diabetes, previous medications were discontinued at trial onset	N=15,245 4.2 years (mean)	Primary: Time to first cardiac event (cardiac morbidity and mortality) Secondary: Fatal and nonfatal myocardial infarction, fatal and nonfatal heart failure and fatal and nonfatal stroke, all-cause mortality, new onset diabetes	Primary: There were no differences in the primary composite end point between the valsartan and amlodipine groups (10.6% vs 10.4%; *P*=0.49). Secondary: There was a higher incidence of myocardial infarction (4.8% vs 4.1%; *P*=0.02) in patients receiving valsartan than amlodipine. There was no difference in the incidence of heart failure (4.6% vs 5.3%; *P*=0.12), stroke (4.2% vs 3.7%; *P*=0.08), and all-cause mortality (11.0% vs 10.8%; *P*=0.45) between valsartan- and amlodipine-treated patients. New onset diabetes occurred less with valsartan (13.1%) vs amlodipine (16.4%; *P*<0.001). Limited benefit of valsartan vs amlodipine was attributed to the differences in blood pressure lowering. Combined target blood pressure (<140/90 mm Hg) was achieved in 58% and 62% of patients receiving valsartan and amlodipine, respectively.
Conlin et al[44] PREVAIL Candesartan 8 to 16 mg/day, irbesartan 150 to 300 mg/day, losartan 50	MA of 43 PC, RCT Trials involved ARBs vs placebo, other antihypertensive classes, and direct comparisons between	N=11,281 Duration varied	Primary: Weighted average for SBP and DBP reduction with ARB monotherapy, dose titration, and with the addition of low-dose	Primary: The absolute weighted-average reductions in DBP (8.2 to 8.9 mm Hg) and SBP (10.4 to 11.8 mm Hg) for ARB monotherapy were comparable for all ARBs (no *P* value reported). Responder rates for ARB monotherapy were 48% to 55%. Dose titration resulted in slightly greater blood pressure reductions

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to 100 mg/day, and valsartan 80 to 160 mg/day vs another ARB vs ARB plus low-dose HCTZ	ARBs		HCTZ were calculated; responder rates Secondary: Not reported	and an increase in responder rates of 53% to 63% (no *P* value reported). ARB and HCTZ combinations produced substantially greater reductions in SBP (16.1 to 20.6 mm Hg) and DBP (9.9 to 13.6 mm Hg) than ARB monotherapy (no *P* value reported). Responder rates for ARB and HCTZ combinations were 56% to 70% (no *P* value reported). The authors concluded that candesartan, irbesartan, losartan and valsartan produced comparable antihypertensive efficacy when administered at their recommended doses, a near flat dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ. Secondary: Not reported
Blood Pressure Lowering Treatment Trialists' Collaboration[45] ACE inhibitors (17 trials) vs angiotensin II receptor antagonists (ARBs) (9 trials)	MA of RCT published by the end of 2004 Patients with high blood pressure, diabetes, history of CHD or cerebrovascular disease	26 large-scale trials, N=146,838 Duration varied	Primary: Nonfatal myocardial infarction or death from CHD, including sudden death; heart failure causing death or requiring hospitalization; nonfatal stroke or death from cerebrovascular disease Secondary: Not reported	Primary: From a total of 146,838 individuals with high blood pressure or an elevated risk of cardiovascular disease, major cardiovascular events were documented in 22,666 patients during follow-up. The analyses showed comparable blood pressure-dependent reductions in risk with ACE inhibitors and ARBs ($P \geq 0.3$ for all 3 outcomes). ACE inhibitors produced a blood pressure-independent reduction in the relative risk of CHD of approximately 9% (95% CI, 3% to 14%). No similar effect was detected for ARBs, and there was some evidence of a difference between ACE inhibitors and ARBs in this regard ($P=0.002$). For both stroke and heart failure, there was no evidence of any blood pressure-independent effects of either ACE inhibitors or ARBs. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The authors concluded that there are similar blood pressure-dependent effects of ACE inhibitors and ARBs for the risks of stroke, CHD and heart failure. For ACE inhibitors but not ARBs, there is evidence of blood pressure–independent effects on the risk of major coronary disease events.
Heart Failure				
Cohn et al[46] Val-HeFT Valsartan 160 mg BID vs placebo	DB, PC, RCT Patients ≥18 years old with a cardiovascular history and NYHA II-IV heart failure	N=5,010 2 years	Primary: Mortality and composite end point of morbidity and mortality Secondary: Change in NYHA class, ejection fraction, signs and symptoms of heart failure, quality of life	Primary: Compared with placebo, valsartan resulted in no significant differences in all-cause mortality. Patients treated with valsartan experienced a 13% decrease in the composite end point (*P*=0.009) and 27% decrease in heart failure hospitalizations (*P*<0.001). Secondary: Treatment with valsartan resulted in significant improvements in NYHA class, ejection fraction, signs and symptoms of heart failure and quality of life as compared with placebo (*P*<0.01). In a post hoc analysis of the combined end point and mortality in subgroups defined according to baseline treatments with ACE inhibitors or β-blockers, valsartan had a favorable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs.
Pfeffer, Swedberg et al[47] CHARM Overall Programme Candesartan 32 mg daily (±ACE inhibitor) vs placebo (±ACE inhibitor)	DB, PC, PG, RCT Summary of all CHARM sub-studies	N=7,599 37.7 months	Primary: All-cause mortality (Overall Programme) and cardiovascular death or hospital admission for CHF (all of the component trials) Secondary: Not reported	Primary: In the overall analysis, candesartan 32 mg daily resulted in an 18% decreased risk of all-cause mortality compared to placebo (23% vs 25%; unadjusted HR, 0.91; 95% CI, 0.83 to 1.00; *P*=0.055; covariate adjusted HR, 0.90; 95% CI, 0.82 to 0.99; *P*=0.032). Annual mortality rates were 8.1% and 8.8% for patients treated with candesartan and placebo, respectively. The lower mortality in patients treated with candesartan vs placebo was attributed to fewer cardiovascular deaths (18% vs 20%; unadjusted HR, 0.88; 95% CI, 0.79 to 0.97; *P*=0.012).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Hospital admissions for CHF were significantly fewer in patients treated with candesartan than placebo (20% vs 24%; *P*<0.0001). Secondary: Not reported
McMurray et al[48] CHARM-Added Candesartan 32 mg daily in patients already taking ACE inhibitors vs placebo in patients already taking ACE inhibitors	DB, MC, PC, RCT Patients ≥18 years old with LVEF ≤40%, NYHA II-IV heart failure and treatment with an ACE inhibitor at a constant dose for 30 days or longer	N=2,548 41 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and myocardial infarction, nonfatal stroke and coronary revascularization	Primary: Compared to placebo, candesartan 32 mg daily when added to ACE inhibitors resulted in a 15% reduction in the primary end point (*P*=0.011), 16% decrease in cardiovascular deaths (*P*=0.029) and 17% reduction in heart failure hospitalizations (*P*=0.014). Secondary: Fewer patients experienced cardiovascular death, hospital admission for CHF, myocardial infarction, stroke, or coronary revascularization in the candesartan group (42.9%) compared to placebo (46.9%; *P*=0.015).
Granger et al[49] CHARM-Alternative Candesartan 32 mg daily vs placebo	DB, PC, RCT Patients ≥18 years old with LVEF ≤40%, NYHA II-IV heart failure and intolerance to ACE inhibitors	N=2,028 33.7 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and myocardial infarction, nonfatal stroke and coronary revascularization	Primary: Compared to placebo, candesartan 32 mg daily resulted in a 30% reduction of the composite end point (*P*<0.0001). A 20% decrease in cardiovascular death (*P*=0.02) and 39% reduction in heart failure hospitalizations (*P*<0.0001) were noted in patients treated with candesartan compared to placebo. Study drug discontinuation rates were similar in the candesartan (30%) and placebo (29%) groups. Secondary: Fewer patients experienced cardiovascular death, hospital admission for CHF, myocardial infarction, stroke, or coronary revascularization in the candesartan group (39.1%) compared to placebo (44.9%; *P*<0.0001).
Yusuf et al[50] CHARM-Preserved	DB, PC, RCT Patients ≥18 years old	N=3,025 36.6 months	Primary: Composite of cardiovascular death	Primary: Compared to placebo, candesartan 32 mg daily resulted in an insignificant 14% trend towards lower incidence of the primary end

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Candesartan 32 mg daily vs placebo	with preserved ejection fraction (>40%) and symptomatic heart failure		and hospitalization for heart failure Secondary: Composites of primary end point and myocardial infarction, nonfatal stroke and coronary revascularization	point (*P*=0.051). Candesartan significantly reduced the risk of heart failure hospitalization (16%; *P*=0.047) but did not significantly decrease the risk of cardiovascular death (*P*=0.635). Secondary: The composite of cardiovascular death, hospitalization for CHF, myocardial infarction and stroke was significantly lower in the candesartan group compared to placebo (25.6% vs 28.4%; *P*=0.037). There was no significant difference in the composite of cardiovascular death, hospital admission for CHF, myocardial infarction, stroke, or coronary revascularization in the candesartan group (30.4%) compared to placebo (32.9%; *P*=0.130).
Pitt, Segal et al[51] ELITE Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥65 years with symptomatic heart failure (NYHA class II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=722 1 year	Primary: Change in renal function Secondary: Composite of death and/or hospital admission for heart failure, all-cause mortality, admission for heart failure, NYHA class, admission for myocardial infarction or unstable angina	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups). Secondary: Death and/or hospital admission for heart failure was recorded in 9.4% of patients receiving losartan and 13.2% for patients receiving captopril (risk reduction, 32%; 95% CI, –4% to +55%; *P*=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8% vs 8.7%; risk reduction, 46%; 95% CI, 5% to 69%; *P*=0.035). Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline. Admission to the hospital for any reason was less frequent with losartan than with captopril treatment (22.2% vs 29.7%; *P*=0.014). More patients discontinued therapy due to adverse events with captopril (20.8%) than losartan (12.2%; *P*=0.002).
Pitt, Poole-Wilson et al[52]	DB, MC, PG, RCT	N=3,152	Primary: All-cause mortality	Primary: No significant difference in all-cause mortality was reported between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ELITE II Captopril 50 mg TID vs losartan 50 mg QD	Patients ≥60 years old with symptomatic heart failure (NYHA II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	555 days (mean follow-up)	Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	losartan (17.7%) and captopril (15.9%; HR, 1.13; 95% CI, 0.95 to 1.35; *P*=0.16). Secondary: Sudden death or resuscitated cardiac arrest was observed in 9.0% of patients receiving losartan and 7.3% of patients receiving captopril (HR, 1.25; 95% CI, 0.98 to 1.60; *P*=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse events (9.7% vs 14.7%; *P*<0.001), including cough (0.3% vs 2.7%). Note: The ELITE II trial was a larger follow-up trial to the ELITE I trial to confirm the secondary end point from the ELITE I trial which reported a greater reduction in all-cause mortality with losartan compared with captopril.
McKelvie et al[53] RESOLVD Pilot Study Enalapril 10 mg BID vs candesartan 4 to 16 mg QD vs combination candesartan 4 to 8 mg QD and enalapril 10 mg BID	DB, PG, MC, RCT Patients with CHF (NYHA classes II to IV), a 6 minute walk distance of 500 meters or less, and an ejection fraction <40%	N=768 43 weeks	Primary: Change in 6-minute walk distance Secondary: Change in NYHA functional class, quality of life, ejection fraction, ventricular volumes, neurohormone levels, safety	Primary: There were no significant differences among the groups with regards to the 6-minute walk distance over the 43-week study period (*P* value not reported). Secondary: There were no significant differences among the groups with regards to the NYHA functional class or quality of life at 18 or 43 weeks (*P* values not reported). Ejection fraction increased more with candesartan plus enalapril than monotherapy with either agent; however, the difference was not statistically significant (*P*=NS). End-diastolic volumes (*P*<0.01) and end-systolic volumes (*P*<0.05) increased less with combination therapy than with monotherapy with either agent. Aldosterone decreased with combination therapy at 17 but not 43 weeks compared with candesartan or enalapril (*P*<0.05). Brain natriuretic peptide decreased with combination therapy compared with candesartan and enalapril alone (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Blood pressure decreased with combination therapy compared with candesartan or enalapril alone (*P*<0.05). Compared with enalapril, potassium levels decreased with candesartan use (*P*<0.05) and increased with candesartan plus enalapril (*P*<0.05). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups. There were no significant differences in creatinine, mortality, or hospitalizations for CHF or any cause among the 3 groups.
Lee et al[54] ARBs vs placebo (+/-ACE inhibitor) vs ACE inhibitor monotherapy	MA of 24 DB, PC, RCT Patients with chronic heart failure and high-risk acute myocardial infarction	N=38,080 Duration varied	Primary: All-cause mortality and heart failure hospitalizations Secondary: Not reported	Primary: ARBs were associated with reduced all-cause mortality (OR, 0.83) and heart failure hospitalizations (OR, 0.64) vs placebo. There was no difference in all-cause mortality (OR, 1.06) and heart failure hospitalization (OR, 0.95) between ARBs and ACE inhibitors. When ARBs were combined with ACE inhibitors, all-cause mortality was not reduced (OR, 0.97) but heart failure hospitalizations were reduced (OR, 0.77) compared to treatment with ACE inhibitors alone. Two RCT comparing ARBs with ACE inhibitors in patients with high-risk acute myocardial infarction did not reveal differences in all-cause mortality or heart failure hospitalization. Secondary: Not reported
Post–Myocardial Infarction				
Pfeffer, McMurray, et al[55] VALIANT Captopril 50 mg TID	DB, MC, RCT Men and women ≥18 years with an acute myocardial infarction that was complicated by clinical or radiologic	N=14,703 24.7 months	Primary: All-cause mortality Secondary: Death from cardiovascular causes, recurrent	Primary: No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (*P*=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (*P*=0.73).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs valsartan 160 mg BID vs combination valsartan 80 mg BID and captopril 50 mg TID	signs of heart failure and/or evidence of left ventricular systolic dysfunction		myocardial infarction, hospitalization for heart failure	Secondary: The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (*P*=0.20). The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (*P*=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash, and taste disturbance were more common in the captopril group.
Dickstein et al[56] OPTIMAAL Losartan 50 mg QD vs captopril 50 mg TID	DB, MC, PG, RCT Patients ≥50 years (mean age 67.4 years) with an acute myocardial infarction and signs or symptoms of heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction	N=5,477 2.7 years (mean)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between patients receiving losartan and captopril (18% vs 16%, respectively; RR, 1.13; 95% CI, 0.99 to 1.28; *P*=0.07). Secondary: No significant difference in sudden cardiac death or resuscitated cardiac arrest was reported between patients receiving losartan and captopril (9% vs 7%; RR, 1.19; 95% CI, 0.98 to 1.43; *P*=0.07). Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (17% vs 23%; *P*<0.0001).
Renal Dysfunction				
Mogensen et al[57] CALM Lisinopril 20 mg QD vs candesartan 16 mg QD	DB, DD, MC, PG, RCT Patients 30 to 75 years old with hypertension, type 2 diabetes, and microalbuminuria	N=199 24 weeks	Primary: Blood pressure and urinary albumin:creatinine ratio Secondary: Not reported	Primary: At 12 weeks, mean reductions in DBP were 9.7 mm Hg (*P*<0.001) and 9.5 mm Hg (*P*<0.001), respectively, and in urinary albumin:creatinine ratio were 46% (*P*<0.001) and 30% (*P*<0.001) for lisinopril and candesartan, respectively. Compared to either agent alone, at 24 weeks the combination of lisinopril plus candesartan resulted in 16.3 mm Hg reduction in mean DBP vs 10.4 mm Hg for candesartan alone (*P*<0.001) and 10.7 mm

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs lisinopril 20 mg QD plus candesartan 16 mg QD Patients received 12 weeks monotherapy followed by an additional 12 weeks of monotherapy or combination therapy.				Hg for lisinopril alone (*P*<0.001). The reduction in urinary albumin:creatinine ratio with combination treatment (50%) was greater than with lisinopril alone (39%; *P*<0.001) and candesartan alone (24%; *P*=0.05). All treatments were generally well tolerated. Secondary: Not reported
Lewis et al[58] IDNT Irbesartan 300 mg daily vs amlodipine 10 mg daily vs placebo	DB, MC, PC, PRO, RCT Patients 30-70 years old, with type 2 diabetes mellitus, hypertension, and nephropathy	N=1,715 2.6 years	Primary: Composite of risk of doubling serum creatinine, ESRD, or death from any cause Secondary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, heart failure requiring hospitalization, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation	Primary: Compared to placebo, irbesartan 300 mg daily resulted in a 20% lower relative risk of the composite primary outcome (*P*=0.02). Irbesartan treatment was associated with a 33% lower risk of doubling serum creatinine (*P*=0.003) and 23% trend towards lower risk of ESRD (*P*=0.07) compared to placebo. There was no significant difference in risk of death from any cause for irbesartan compared to placebo (*P*=0.57). Compared to amlodipine, irbesartan treatment resulted in a 23% lower risk of composite primary outcome (*P*=0.006). Irbesartan treatment was associated with a 37% lower risk of doubling serum creatinine vs amlodipine (*P*<0.001) and 23% trend towards lower risk of ESRD vs amlodipine (*P*=0.07). There was no significant difference in risk of death from any cause (*P*=0.80). Secondary: There were no significant differences in the secondary cardiovascular composite end point (*P*=0.40 and *P*=0.79 for irbesartan vs placebo and amlodipine, respectively).
Parving, Lehnert et al[59] IRMA2 Irbesartan 150 or 300	DB, MC, PC, RCT Patients with hypertension, type 2 diabetes mellitus and	N=590 2 years	Primary: Time to onset of diabetic nephropathy Secondary:	Primary: The primary end point was reached in 5.2% of patients in the irbesartan 300 mg group (*P*<0.001) and 9.7% of patients in the irbesartan 150 mg group (*P*=0.08) compared to 14.9% of patients receiving placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day vs placebo	microalbuminuria		Changes in level of albuminuria and creatinine clearance and restoration of normoalbuminuria	Secondary: Irbesartan reduced the level of urinary albumin excretion by 38% in patients receiving the 300 mg dose and 24% in patients receiving the 150 mg dose vs 2% for placebo (*P*<0.001 for the combined irbesartan groups vs placebo and *P*<0.001 for the 300 vs 150 mg doses). There was no significant difference in the decline in creatinine clearance among the 3 groups. Restoration of normoalbuminuria was observed in 34% of patients receiving irbesartan 300 mg (*P*=0.006), 24% of patients receiving irbesartan 150 mg (no *P* value reported) and 21% with placebo.
Brenner et al[60] RENAAL Losartan 50 to 100 mg QD vs placebo	DB, PC, RCT Patients 31-70 years of age with hypertension, type 2 diabetes mellitus and nephropathy on conventional antihypertensive therapy	N=1,513 3.4 years	Primary: Composite of risk of doubling of serum creatinine, ESRD, or death from any cause Secondary: Composite of morbidity and mortality from cardiovascular causes, proteinuria, rate of progression of renal disease	Primary: Compared to placebo, losartan resulted in a 16% reduction of composite primary end point (*P*=0.02). Losartan treatment produced a 25% reduction of doubling serum creatinine vs placebo (*P*=0.006) and 28% reduction in ESRD vs placebo (*P*=0.002). No differences in mortality were reported (*P*=0.88). Secondary: There was no significant difference between the losartan and placebo groups in the composite end point of morbidity and mortality from cardiovascular causes (no *P* value reported). Losartan treatment led to an average reduction in the level of proteinuria by 35% (*P*<0.001 vs placebo). Losartan reduced the rate of decline in renal function by 18% (*P*=0.01 vs placebo).
Hou et al[61] ROAD	OL, PRO, RCT Patients aged 18-70	N=360 3.7 years	Primary: Time to composite of doubling of serum	Primary: Compared with the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Benazepril 10 mg/day vs individual uptitration (10 to 40 mg/day with median dose of 20 mg/day) vs losartan 50 mg/day vs individual uptitration (50 to 200 mg/day with median dose of 100 mg/day) Uptitration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained.	years with proteinuria and chronic renal insufficiency who did not have diabetes	(median follow-up)	creatinine, ESRD or death Secondary: Changes in level of proteinuria, rate of progression of renal disease	uptitration were associated with a 51% and 53% reduction in the risk for the primary end point (*P*=0.028 and *P*=0.022, respectively). There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages (no *P* values reported). Secondary: Optimal antiproteinuric dosages of benazepril and losartan at comparable blood pressure control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared with their conventional dosages. There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages (no *P* values reported). Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (*P*>0.05). There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in any of the treatment arms (no *P* values reported).
Parving, Persson et al[62] AVOID Losartan 100 mg daily plus aliskiren 150 mg daily for 3 months then 300 mg for an additional 3 months vs losartan 100 mg plus	DB, MC, PC, RCT Hypertensive patients who were 18 to 85 years of age who had type 2 diabetes and nephropathy	N=599 6 months	Primary: Reduction in albumin:creatinine ratio at 6 months Secondary: Blood pressure reductions, adverse events	Primary: Treatment with aliskiren 300 mg daily as compared with placebo reduced the mean urinary albumin:creatinine ratio by 20% (95% CI, 9% to 30%; *P*<0.001), with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared with 12.5% of those who received placebo (*P*<0.001). Secondary: A small difference in blood pressure was seen between the treatment groups by the end of the study period with SBP and DBP pressures 2 and 1 mm Hg lower, respectively, in the aliskiren group (*P*=0.07 and *P*=0.08, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				The total numbers of adverse and serious adverse events were similar in the groups.
Barnett et al[63] DETAIL Telmisartan 80 mg/day vs enalapril 20 mg/day	DB, MC, PG, RCT Patients aged 35 to 80 years with type 2 diabetes and hypertension	N=250 5 years	Primary: Change in the GFR Secondary: Annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; rates of ESRD and cardiovascular events; all-cause mortality	Primary: After 5 years, GFR decreased by 17.9 mL/minute/1.73 m^2 with telmisartan compared to 14.9 mL/min/1.73 m^2 with enalapril (mean difference, –3.0 mL/min/1.73 m^2; 95% CI, –7.6 to 1.6 mL/min/1.73m^2). Therefore, the changes in GFR were comparable between the groups (*P* value not specified). Secondary: The effects of the 2 agents on the secondary end points were not significantly different after 5 years.
Galle et al[64] Telmisartan 80 mg QD vs valsartan 160 mg QD Additional antihypertensive therapy was permitted.	DB, MC, PG, PRO, RCT, noninferiority study Hypertensive patients (SBP/DBP >130/80 mm Hg) with type 2 diabetes, proteinuria and serum creatinine ≤3.0 mg/dL	N=885 12 months	Primary: Change from baseline in the 24-hour proteinuria Secondary: Changes in 24-hour albuminuria, estimated GFR and inflammatory parameters	Primary: Telmisartan and valsartan produced comparable reductions in 24-hour urinary protein excretion rates: geometric mean reduction was 33% for both telmisartan and valsartan. Secondary: No significant differences between treatments were seen in changes from baseline in 24-hour urinary albumin excretion rate and GFR at 12 months. With both treatments, greater renoprotection was seen among patients with better blood pressure control. No significant changes in C-reactive protein were noted for either group at 12 months.
Viberti et al[65] MARVAL Valsartan 80 mg/day	AC, DB, RCT Patients 35-75 years old with type 2 diabetes mellitus and microalbuminuria, with	N=332 24 weeks	Primary: Change in UAER; proportion of patients who returned to normal albuminuria	Primary: Valsartan resulted in a UAER reduction of 44% at 24 weeks compared to baseline vs an 8% reduction with amlodipine (*P*<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amlodipine 5 mg/day A target blood pressure of 135/85 mm Hg was aimed for by dose-doubling followed by the addition of bendrofluazide* and doxazosin whenever needed.	or without hypertension		Secondary: Proportion of patients returning to normoalbuminuria	Over the study period, blood pressure reductions were similar between the 2 treatments and at no time point was there a between-group significant difference in blood pressure values in either the hypertensive or the normotensive subgroup. Secondary: The proportion of patients returning to normal albuminuria was greater with valsartan (29.9%) vs amlodipine (14.5%; *P*=0.001).
Casas et al[66] ACE inhibitor or ARBs compared with placebo vs ACE inhibitor or ARBs compared with other antihypertensive drugs (β-blockers, α-adrenergic blocking agents, CCB's, or combinations) Specific agents and doses were not specified.	MA of RCT (searched up to January 2005), parallel-design Studies in adults that examined the effect of any drug treatment with a blood pressure-lowering action on progression of renal disease	N=127 studies 4.2 years (mean)	Primary: Doubling of serum creatinine, ESRD Secondary: Serum creatinine, urine albumin excretion, GFR	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (*P*=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (*P*=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (*P*=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitors or ARBs were reported when these agents were compared to other antihypertensives (*P*=0.001). Compared with other drugs, ACE inhibitors or ARBs had no effect on the GFR (no *P* value reported). Conclusion: Benefits of ACE inhibitors or ARBs on renal outcomes compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				with placebo are probably due to a blood pressure-lowering effect. In diabetic patients, additional renoprotective effects of ACE inhibitors or ARBs beyond blood pressure lowering remain unproven and there is uncertainty about the greater renoprotection seen in nondiabetic renal disease.
Strippoli, Bonifati et al[67] ACE inhibitors vs placebo (38 trials) or ARBs vs placebo (4 trials) or ACE inhibitors vs ARBs (7 trials)	MA of 49 RCT (to December 2005) Patients with diabetic kidney disease	N=12,067 Duration at least 6 months	Primary: All-cause mortality, ESRD, doubling of serum creatinine concentration, progression from micro- to macroalbuminuria, regression from micro- to normoalbuminuria, drug-related toxicity (including cough, headache, hyperkalemia, impotence and pedal edema) Secondary: Not reported	Primary: There was no significant difference in the risk of all-cause mortality for ACE inhibitors vs placebo or no treatment (RR, 0.91; 95% CI, 0.71 to 1.17) and ARBs vs placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17). No statistically significant reduction in the risk of all-cause mortality was found in the 3 studies that compared ACE inhibitors with ARBs (RR, 0.92; 95% CI, 0.31 to 2.78). A subgroup analysis of studies showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACE inhibitors (RR, 0.78; 95% CI, 0.61 to 0.98) but not when using half or less than half the maximum tolerable dose of ACE inhibitors (RR, 1.18; 95% CI, 0.41 to 3.44). There was a significant reduction in the risk of ESRD with ACE inhibitors and ARBs compared to placebo or no treatment (RR, 0.60; 95% CI, 0.39 to 0.93 and RR, 0.78; 95% CI, 0.67 to 0.91, respectively). There was a significant reduction in the risk of doubling of serum creatinine concentration with ACE inhibitors and ARBs (RR, 0.68; 95% CI, 0.47 to 1.00 and RR, 0.79; 95% CI, 0.67 to 0.93, respectively). ACE inhibitors and ARBs significantly reduced the risk of progression from micro- to macroalbuminuria (RR, 0.45; 95% CI, 0.29 to 0.69 and RR, 0.49; 95% CI, 0.32 to 0.75, respectively). ACE inhibitors and ARBs significantly increased the regression from micro- to normoalbuminuria compared to placebo or no treatment (RR, 3.06; 95% CI, 1.76 to 5.35 and RR, 1.42; 95% CI, 1.05 to 1.93, respectively). The 7 studies that compared ACE inhibitors to ARBs did not report the outcome of ESRD or doubling of serum creatinine. Progression

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				from micro- to macroalbuminuria and from micro- to normoalbuminuria were evaluated each in 1 trial and showed a nonsignificant difference in the risk between ACE inhibitors and ARBs. ACE inhibitors were associated with a significant increase in the risk of cough but not hyperkalemia, headache or impotence when compared to placebo or no treatment. ARBs were associated with a significant increase in the risk of hyperkalemia but not cough or headache compared to placebo or no treatment. Secondary: Not reported
Other Studies				
Papademetriou et al[68] SCOPE Candesartan 16 mg/day vs placebo in addition to conventional therapy (diuretics, ACE inhibitors, β-blockers, CCBs)	DB, MC, PC, PG, RCT Patients 70-89 years old with isolated systolic hypertension (SBP >160 mm Hg and DBP <90 mm Hg) and MMSE scores ≥24	N=1,518 3.7 years	Primary: First major coronary event including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke Secondary: cardiovascular death, nonfatal and fatal stroke and myocardial infarction	Primary: There was no difference in the first major cardiovascular event between patients (with isolated systolic hypertension) who were treated with candesartan vs placebo (RR, 0.89; 95% CI, 0.65 to 1.21; *P*>0.20). Secondary: A total of 20 fatal/nonfatal strokes occurred in the candesartan group and 35 in the control group (RR, 0.58; 95% CI, 0.33 to 1.00) for a RR reduction of 42% (*P*=0.050 unadjusted and *P*=0.049 adjusted for baseline risk). There were no marked or statistically significant differences between the treatment groups in other cardiovascular end points or all-cause mortality.
Fliser et al[69] EUTOPIA Olmesartan 20 mg/day and after 6 weeks, pravastatin 20 mg/day daily was added	DB, PC, PG, RCT Patients ≥18 years old with hypertension, atherosclerotic disease, type 2 diabetes mellitus, and/or LDL-C between 3.89 to 6.48	N=199 12 weeks	Primary: Evaluate anti-inflammatory effects of olmesartan using a panel of inflammation markers: high-sensitivity C-reactive	Primary: After 6 weeks of therapy, olmesartan treatment significantly reduced serum levels of C-reactive protein (–15.1%; *P*<0.05), tumor necrosis factor-α (–8.9%; *P*<0.02), interleukin-6 (–14.0%; *P*<0.05) and monocyte chemotactic protein-1 (–6.5%; *P*<0.01), whereas placebo treatment had no major effect on inflammation markers. After 12 weeks of therapy, C-reactive protein (–21.1%; *P*<0.02),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo and after 6 weeks, pravastatin 20 mg/day was added	mmol/L		protein, high-sensitivity tumor necrosis factor-α, interleukin-6 Secondary: Not reported	tumor necrosis factor-α (–13.6%; *P*<0.01), and interleukin-6 (–8.0%; *P*<0.01) decreased further with olmesartan and pravastatin cotherapy, but treatment with pravastatin alone did not significantly alter inflammation markers. In contrast, addition of pravastatin led to a significant (*P*<0.001) reduction in LDL-C in the olmesartan and placebo groups (–15.1% and –12.1%, respectively). Secondary: Not reported
ONTARGET Investigators[70] Ramipril 10 mg/day vs telmisartan 80 mg/day vs ramipril 10 mg/day and telmisartan 80 mg/day	DB, MC, PC, RCT Men and women (mean age 66.4 years in the ramipril and telmisartan monotherapy arms and 66.5 years in the combination arm) with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	N=25,620 56 months (median follow-up)	Primary: Death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure Secondary: Composite of death from cardiovascular causes, myocardial infarction or stroke; heart failure, worsening or new angina, new diagnosis diabetes mellitus, new atrial fibrillation, renal impairment, revascularization procedures	Primary: The primary outcome occurred in 16.5%, 16.7% and 16.3% of patients receiving ramipril, telmisartan and combination therapy, respectively (*P* values not reported). Secondary: The composite of death from cardiovascular causes, myocardial infarction or stroke occurred in 14.1% of patients in the ramipril group and 13.9% of patients in the telmisartan group (RR, 0.99; 95% CI, 0.91 to 1.07; *P*=0.001 for noninferiority). Combination therapy was not significantly better than ramipril alone (RR, 0.99; 95% CI, 0.92 to 1.07). There were no significant differences in the rates of secondary outcomes, except for renal dysfunction, which occurred in 10.2% of patients receiving ramipril, 10.6% of patients receiving telmisartan and 13.5% of patients receiving combination therapy (*P*<0.001 vs ramipril; no *P* value reported vs telmisartan). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs 4.2%; *P*<0.001) and angioedema (0.1% vs 0.3%; *P*=0.01) and a higher rate of hypotensive symptoms (2.6% vs 1.7%; *P*<0.001); the rate of syncope was the same in the 2 groups (0.2%). As compared with the ramipril group, combination therapy had an

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				increased risk of hypotensive symptoms (4.8% vs 1.7%; *P*<0.001), syncope (0.3% vs 0.2%; *P*=0.03) and renal dysfunction (13.5% vs 10.2%; *P*<0.001).

Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: AC=active comparator, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ABPM=ambulatory blood pressure monitoring, ARB=angiotensin II receptor antagonist, β-blockers=β-adrenergic blocking agents, CAD=coronary artery disease, CCBs=calcium channel blocking agents, CHD=coronary heart disease, CHF=congestive heart failure, DBP=diastolic blood pressure, ESRD=end-stage renal disease, GFR=glomerular filtration rate, LDL-C=low-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, LVH=left ventricular hypertrophy, MAP=mean arterial pressure, MMSE=Mini Mental State Examination, NYHA=New York Heart Association, SBP=systolic blood pressure, UAER=urinary albumin excretion rate, WMD=weighted mean difference

Additional Evidence

Dose Simplification:
. An evidence-based medicine literature search did not reveal any additional data pertinent to this topic.

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity Angiotensin II Receptor Antagonists

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
candesartan	tablet	Atacand®	$$$	N/A
eprosartan	tablet	Teveten®	$$$	N/A
irbesartan	tablet	Avapro®	$$$	N/A
losartan	tablet	Cozaar®	$$$	N/A
olmesartan	tablet	Benicar®	$$$	N/A
telmisartan	tablet	Micardis®	$$$	N/A
valsartan	tablet	Diovan®	$$$	N/A

No generic products are available in this class.
N/A=not available.

X. Conclusions

There are 7 angiotensin II receptor antagonists or blockers (ARBs) currently on the market and none of them are available generically. All of the ARBs are Food and Drug Administration (FDA)-approved for the treatment of hypertension. As with the Angiotensin Converting Enzyme (ACE) inhibitors, compelling indications for initial treatment of hypertension with ARBs include heart failure, diabetes, diabetic nephropathy, chronic kidney disease, left ventricular hypertrophy, and myocardial infarction.[13-20] In the treatment of hypertension, meta-analyses of comparative trials involving different ARBs showed slight differences in blood pressure-lowering

ability between these agents; however, the clinical significance of these differences remains to be established.[40,41] In one meta-analysis of ARB trials in hypertension, the authors' overall conclusion was that all ARBs included in this analysis demonstrated comparable blood pressure lowering when administered at their usual recommended doses.[44] Current consensus guidelines do not give preference to one ARB over another for the management of hypertension.

Candesartan and valsartan are also FDA approved for the treatment of heart failure. These agents have demonstrated comparable morbidity and mortality benefit when compared to ACE inhibitors in several clinical trials. Candesartan has been shown to reduce cardiovascular death and heart failure hospitalization in patients with heart failure and left ventricular systolic dysfunction.[24] Valsartan was shown to reduce hospitalizations for heart failure.[30] Candesartan but not valsartan was shown to have an added effect on outcomes when used with an ACE inhibitor. Although there are only two ARBs with FDA approval for heart failure, it is undetermined whether the clinical benefit is product-specific or a class effect.

The VALIANT trial demonstrated a comparable benefit with valsartan versus captopril, an ACE inhibitor, and this led to valsartan's approval for use in post-myocardial infarction patients.[55] The OPTIMAAL trial demonstrated similar benefit with losartan versus captopril, an ACE inhibitor, in high-risk patients after myocardial infarction.[56] In general, the consensus guidelines recommend the use of ARBs in patients who are intolerant to ACE inhibitor therapy.[21,22] Losartan is the only ARB indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.[37] Additional studies are needed to determine if these clinical benefits are product-specific or a class effect.

Currently, two ARBs, irbesartan and losartan, are approved for use in patients with diabetic nephropathy. Through the IDNT and RENAAL trials, irbesartan and losartan reduced the rate of progression of nephropathy (as measured by occurrence of doubling of serum creatinine or ESRD) in type 2 diabetics with hypertension and diabetic nephropathy with elevated serum creatinine and proteinuria.[58,60] However, clinical benefit in diabetic nephropathy has been shown with other ARBs, including candesartan, telmisartan, and valsartan.[57,59,61,63,64] The American Diabetes Association notes that both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria in patients with type 2 diabetes, hypertension and microalbuminuria.[18] ARBs have been shown to delay the progression of nephropathy in type 2 diabetic patients with macroalbuminuria and renal insufficiency. The ADA recommends either an ACE inhibitor or ARB for the treatment of nonpregnant patients with micro- or macroalbuminuria. If one class is not tolerated, the other should be substituted.

There is currently more data available on patient outcomes, including morbidity and mortality benefit, for ACE inhibitors than for ARBs, particularly with regards to the treatment of hypertension, heart failure, and post-myocardial infarction. In addition, most of the ACE inhibitors, with the exception of perindopril, are available in generic formulations. Comparative data regarding the ARBs has not demonstrated distinct clinically significant differences over ACE inhibitors regarding safety and tolerability when prescribed for general use. Overall, no ARB offers a significant clinical advantage over another when prescribed for general use.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity angiotensin II receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Angiotensin II Receptor Antagonists
Combination Products
AHFS Class 243208
September 10, 2008

I. Overview

The combination angiotensin II receptor antagonists or blockers (ARBs) are products that combine an ARB with hydrochlorothiazide, a thiazide diuretic, in a fixed-dose formulation. All of the combination ARBs are Food and Drug Administration (FDA)-approved for the treatment of hypertension. The fixed-dose combination products containing irbesartan or losartan with hydrochlorothiazide are approved for the initial treatment of hypertension, while the other products are approved for the treatment of hypertension in patients who have had an inadequate response or experienced adverse effects (eg, hypokalemia) with monotherapy. The combination product containing losartan and hydrochlorothiazide is also approved for the treatment of hypertension in patients with left ventricular hypertrophy.

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[1] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[2] Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[1,2] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. The angiotensin-converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator associated with dry cough.[1-3] Since angiotensin II may also be generated through other pathways that do not depend upon ACE (eg, chymase), blockade of angiotensin II by ACE inhibitors is incomplete.[1] ARBs block the angiotensin II receptor subtype AT_1, preventing the negative effects of angiotensin II, regardless of its origin. ARBs do not appear to affect bradykinin.

Hydrochlorothiazide, a thiazide diuretic, increases the excretion of sodium and chloride by inhibiting their reabsorption in the ascending loop of Henle and the early distal tubules of the kidney.[4] The exact antihypertensive mechanism of the thiazide diuretics is unknown, although sodium depletion appears to be an important factor. During initial therapy, cardiac output and extracellular volume decrease. With chronic therapy, cardiac output returns to baseline, peripheral vascular resistance falls, and there is a persistent small reduction in extracellular volume. Thiazide-type diuretics are considered initial therapy for hypertension in most patients who do not have other significant comorbid conditions.

The combination angiotensin II receptor antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products within this class.

Table 1. Combination Angiotensin II Receptor Antagonists Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
candesartan and hydrochlorothiazide	tablet	Atacand HCT®	none
eprosartan and hydrochlorothiazide	tablet	Teveten HCT®	none
irbesartan and hydrochlorothiazide	tablet	Avalide®	Avalide®
losartan and hydrochlorothiazide	tablet	Hyzaar®	Hyzaar®
olmesartan and hydrochlorothiazide	tablet	Benicar HCT®	Benicar HCT®
telmisartan and hydrochlorothiazide	tablet	Micardis HCT®	Micardis HCT®
valsartan and hydrochlorothiazide	tablet	Diovan HCT®	Diovan HCT®

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Treatment guidelines that incorporate the combination angiotensin II receptor antagonists (ARBs) are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Combination Angiotensin II Receptor Antagonists

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)**[5]	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. Angiotensin converting enzyme (ACE) inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant. • The use of fixed-dose combination products was not addressed in this guideline.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[6]	• If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • The use of fixed-dose combination products was not addressed in this guideline.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[7]	• Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, and the combination is likely to be well tolerated.
Treatment Guidelines From the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[8]	• Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment. • The use of fixed-dose combination products was not addressed in this guideline.
National Institute for Health and	• Initial therapy in patients ≥55 years should be a calcium-channel blocking

Clinical Guideline	Recommendation(s)
Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[9]	agent (CCB) or a thiazide diuretic, and in patients <55 years initial therapy should be an ACE inhibitor. If a second medication is required and the initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • The use of fixed-dose combination products was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes–2008**[10]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is >50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73m^2. • Multiple drug therapy is generally required to achieve blood pressure goals. • The use of fixed-dose combination products was not addressed in this guideline.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[11]	• All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB or ARB plus diuretic. • The use of fixed-dose combination products was not addressed in this guideline.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[12]	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence. • Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the combination angiotensin II receptor antagonists (ARBs) 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 Combination Angiotensin II Receptor Antagonists[13-19]

Drugs	Hypertension	Hypertension With Left Ventricular Hypertrophy
Candesartan and HCTZ	✔ *	
Eprosartan and HCTZ	✔ *	

Drugs	Hypertension	Hypertension With Left Ventricular Hypertrophy
Irbesartan and HCTZ	✔ †	
Losartan and HCTZ	✔ ‡	✔ (to reduce the risk of stroke)§
Olmesartan and HCTZ	✔ *	
Telmisartan and HCTZ	✔ *	
Valsartan and HCTZ	✔ *	

HCTZ=hydrochlorothiazide.
*This fixed-dose combination is not indicated for initial therapy.
†Avalide is indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.

IV. Pharmacokinetics

The pharmacokinetic parameters for the combination angiotensin II receptor antagonists (ARBs) are summarized in Table 4. The combination products have similar pharmacokinetic profiles as their individual components.

Table 4. Pharmacokinetic Parameters of the Combination Angiotensin II Receptor Antagonists (ARBs)[31,32]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Single Entity ARBs						
Candesartan	~15	>99	CYP2C9	Yes; CV-11974	Feces (~67); renal (~33)	~9
Eprosartan	~13	~98	Glucuronidation	No	Feces (~90); renal (~7)	5-9
Irbesartan	60-80	90	CYP2C9	No	Feces (65); renal (20)	11-15
Losartan	25-35	99	CYP2C9; CYP3A4	Yes; 5-carboxylic acid (E-3174)	Feces (50-60); renal (13-35)	~2 (6-9)*
Olmesartan	~26	99	Deesterification	Yes; RNH-6270 (deesterified olmesartan)	Feces (50-65); renal (35-50)	~13
Telmisartan	42-58	>99.5	Conjugation	No	Feces (>97)	~24
Valsartan	~25	95	Minimal	No	Feces (~83); renal (~7-13)	~6-9
Thiazide Diuretics						
Hydrochloro-thiazide	~50-75	40-68	Not appreciably metabolized	Not reported	Renal (50-70)	6-15

*Metabolite

V. Drug Interactions

Combination angiotensin II receptor antagonists (ARBs) share the same drug interactions as their individual components. Significant drug interactions with the combination angiotensin II receptor antagonists are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Combination Angiotensin II Receptor Antagonists[31]

Drug(s)	Significance Level	Interaction	Mechanism
Candesartan, eprosartan, irbesartan, losartan,	1	Potassium-sparing diuretics (amiloride, spironolactone,	Angiotensin II receptor antagonists and potassium-sparing diuretics may increase serum potassium levels, leading to additive or synergistic effects.

Drug(s)	Significance Level	Interaction	Mechanism
olmesartan, telmisartan, valsartan		triamterene)	
Hydrochlorothiazide	1	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Hydrochlorothiazide	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Hydrochlorothiazide	2	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Hydrochlorothiazide	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate carefully in small or intermittent doses.
Hydrochlorothiazide	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.
Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan	2	Lithium	Angiotensin II receptor antagonists may decrease lithium renal excretion by enhancing its reabsorption. Lithium levels may increase, resulting in an increase in pharmacologic and toxic effects of lithium.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the combination angiotensin II receptor antagonists (ARBs) are noted in Table 6. The black box warning regarding the use of combination ARBs during pregnancy is summarized in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Combination Angiotensin II Receptor Antagonists[4,20]

Adverse Event	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan	Hydrochloro-thiazide
Central Nervous System								
Anxiety/nervousness	≥0.5	<1	≥1	<1	-	>0.3	>0.2	-
Depression	≥0.5	1	<1	<1	-	>0.3	-	-
Dizziness	4	≥1	≥1	3.5	3	1	>1	-
Fatigue	>1	2	4	-	>0.5	1	2	-
Headache	≥1	≥1	≥1	≥1	>1	1	>1	-
Insomnia	-	<1	-	1.4	>0.5	>0.3	>0.2	-
Gastrointestinal								
Abdominal pain	>1	2	≥1	≥1	>0.5	1	2	-
Anorexia	-	-	-	-	-	-	-	1-10
Diarrhea	>1	≥1	3	2.4	>1	3	>1	-
Dyspepsia/heartburn	≥0.5	≥1	2	1.3	>0.5	1	>0.2	1-10
Hepatic function impaired	-	-	-	-	-	-	-	<1
Nausea/vomiting	>1	<1	≥1	≥1	>0.5	1	>1	-
Musculoskeletal								
Arthralgia	>1	2	-	<1	>0.5	>0.3	>1	-
Muscle cramp	-	-	-	1.1	-	-	>0.2	-
Myalgia	≥0.5	≥1	-	1	>0.5	1	>0.2	-
Pain (includes back and leg)	3	<1	≥1	1-1.8	>1	1-3	>0.2	-
Trauma	-	-	2	-	-	-	-	-
Respiratory								
Bronchitis	>1	≥1	-	<1	>1	>0.3	-	-
Cough	>1	4	2.8	3.4	-	1	>1	-
Eosinophilic pneumonitis	-	-	-	-	-	-	-	<1
Influenza/influenza-like symptoms	-	<1	≥1	<1	>1	1	-	-
Nasal congestion	-	-	-	2	-	-	-	-
Pharyngitis	2	4	≥1	≥1	>1	1	>1	-
Respiratory distress	-	-	-	-	-	-	-	<1
Rhinitis	2	4	≥1	<1	>1	>0.3	>1	-
Sinus disorder	-	-	≥1	1.5	-	-	-	-

Adverse Event	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan	Hydrochloro-thiazide
Sinusitis	>1	≥1	-	1	>1	3	>1	-
Upper respiratory tract infection	6	8	9	7.9	>1	7	>1	-
Miscellaneous								
Agranulocytosis	-	-	-	-	-	-	-	<1
Albuminuria	>1	<1	-	-	-	-	-	-
Allergic reactions	✔	✔	✔	✔	✔	✔	✔	<1
Alopecia	-	-	-	-	-	-	-	<1
Anemia	-	-	-	-	-	-	-	<1
Angioedema	✔	✔	✔	✔	✔	✔	✔	-
Chest pain	>1	≥1	≥1	≥1	>0.5	1	-	-
Edema	-	≥1	≥1	≥1	-	-	>1	-
Elevated creatine phosphokinase	≥0.5	<1	-	-	>1	-	-	-
Erythema multiforme	-	-	-	-	-	-	-	<1
Exfoliative dermatitis	-	-	-	-	-	-	-	<1
Hematuria	≥0.5	<1	-	-	>1	-	-	-
Hypercalcemia	-	-	-	-	-	-	-	<1
Hyperglycemia	≥0.5	<1	-	-	>1	-	-	-
Hyperkalemia	✔	-	rare	✔	-	-	✔	-
Hypertension	-	-	<1	-	-	-	-	-
Hypertriglyceridemia	≥ 0.5	1	-	-	>1	-	-	-
Hypokalemia	-	✔	-	-	-	-	-	1-10
Hypotension	-	<1	0.4	<1	-	-	<1	1-10
Inflicted injury	-	2	-	-	>1	-	-	-
Interstitial nephritis	-	-	-	-	-	-	-	<1
Leukopenia	-	-	-	-	-	-	-	<1
Orthostatic hypotension	-	✔	✔	-	-	-	-	1-10
Pancreatitis	-	-	-	-	-	-	-	<1
Peripheral edema	>1	-	-	-	>0.5	1	-	-
Photosensitivity	-	-	-	-	-	-	-	1-10
Rash	≥0.5	<1	≥1	<1	>0.5	>0.3	>0.2	-
Renal failure	-	-	-	-	-	-	-	<1
Stevens-Johnson syndrome	-	-	-	-	-	-	-	<1
Tachycardia	≥0.5	<1	≥1	<1	>0.5	>0.3	-	-
Thrombocytopenia	-	-	-	-	-	-	-	<1
Toxic epidermal necrolysis	-	-	-	-	-	-	-	<1
Urinary tract infection	-	4	≥1	<1	>0.5	1	-	-
Viral infection	-	2	-	-	-	-	3	-

- Event not reported or incidence <1%.
✔ Percent not specified.

Table 7. Black Box Warning for the Combination Angiotensin II Receptor Antagonists[24-30]

WARNING: USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, the combination angiotensin II receptor antagonist should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

VII. Dosing and Administration

The usual dosing regimens for the combination angiotensin II receptor antagonists (ARBs) are summarized in Table 8.

Table 8. Usual Dosing for the Combination Angiotensin II Receptor Antagonists[24-30]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Candesartan and HCTZ	Hypertension: Fixed-combination is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; patients not controlled or experiencing hypokalemia on HCTZ 25 mg can expect an incremental effect from Atacand HCT® 16 mg-12.5 mg; patients not controlled on Atacand® 32 mg can expect incremental blood pressure effects from Atacand HCT® 32 mg-12.5 mg and then 32 mg-25 mg	Safety and efficacy in children have not been established.	Tablet: 16 mg-12.5 mg 32 mg-12.5 mg
Eprosartan and HCTZ	Hypertension: Fixed-combination is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; usual recommended dose is eprosartan 600 mg-HCTZ 12.5 mg once daily when used in patients who are not volume-depleted; patients may be titrated to 600 mg-25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 600 mg-12.5 mg 600 mg-25 mg
Irbesartan and HCTZ	Hypertension: Initial: irbesartan 150 mg-HCTZ 12.5 mg once daily; maximum: 300 mg-25 mg once daily; in patients not controlled on monotherapy with irbesartan or HCTZ, the recommended doses of Avalide® in order of increasing mean effect are 150 mg-12.5 mg, 300 mg-12.5 mg and 300 mg-25 mg; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 150 mg-12.5 mg 300 mg-12.5 mg 300 mg-25 mg
Losartan and HCTZ	Hypertension: Initial: losartan 50 mg-HCTZ 12.5 mg once daily; if blood pressure remains uncontrolled, the dose may be increased to 2 tablets of 50-12.5 mg once daily or 1 tablet of 100 mg-25 mg once daily; maximum 100 mg-25 mg per day Left ventricular hypertrophy in hypertensive patients: Initial: losartan 50 mg once daily; HCTZ 12.5 mg daily should be added or Hyzaar® 50 mg-12.5 mg substituted if blood pressure reduction is inadequate; if additional blood pressure reduction is needed, losartan 100 mg and HCTZ 12.5 mg or Hyzaar® 100 mg-12.5 mg may be substituted, followed by losartan 100 mg and HCTZ 25 mg or Hyzaar® 100 mg-25 mg	Safety and efficacy in children have not been established.	Tablet: 50 mg-12.5 mg 100 mg-12.5 mg 100 mg-25 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Olmesartan and HCTZ	Hypertension: Fixed-combination is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; in patients not controlled on olmesartan, HCTZ may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily; if patient is taking HCTZ, olmesartan may be added starting with a dose of 20 mg once daily and titrated to 40 mg	Safety and efficacy in children have not been established.	Tablet: 20 mg-12.5 mg 40 mg-12.5 mg 40 mg-25 mg
Telmisartan and HCTZ	Hypertension: Fixed-combination is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; patients not controlled on telmisartan 80 mg monotherapy may be switched to Micardis HCT® 80 mg-12.5 mg once daily and titrated up to 160 mg-25 mg if necessary; patients not controlled on HCTZ 25 mg may be switched to Micardis HCT® 80 mg-12.5 mg or 80 mg-25 mg once daily; patients experiencing hypokalemia with HCTZ 25 mg may be switched to Micardis HCT® 80 mg-125 mg once daily	Safety and efficacy in children have not been established.	Tablet: 40 mg-12.5 mg 80 mg-12.5 mg 80 mg-25 mg
Valsartan and HCTZ	Hypertension: Fixed-combination is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; patients not controlled on valsartan monotherapy may switch to Diovan HCT® 80 mg-12.5 mg or 160 mg-12.5 mg once daily; if blood pressure remains uncontrolled, either valsartan or both components may be increased; patients not controlled or experiencing hypokalemia on HCTZ 25 mg may be switched to Diovan HCT® 80 mg-12.5 mg or 160 mg-12.5 mg once daily; maximum: valsartan 320 mg and HCTZ 25 mg	Safety and efficacy in children have not been established.	Tablet: 80 mg-12.5 mg 160 mg-12.5 mg 160 mg-25 mg 320 mg-12.5 mg 320 mg-25 mg

HCTZ=hydrochlorothiazide.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the combination angiotensin II receptor antagonists are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Combination Angiotensin II Receptor Antagonists

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypertension				
McInnes et al[22] Candesartan 8 mg and HCTZ 12.5 mg once daily vs lisinopril 10 mg and HCTZ 12.5 mg once daily	DB, DD, MC, PG, RCT Patients aged 20-80 years with mild-to-moderate hypertension on prior antihypertensive monotherapy	N=355 26 weeks	Primary: Mean changes in DBP Secondary: Mean changes in SBP and heart rate, proportion of responders and controlled patients, safety	Primary: Changes in mean sitting DBP did not differ significantly between the groups (mean difference, 0.5 mm Hg; *P*=0.20). Secondary: No significant differences between the groups were reported for mean sitting SBP, heart rate, proportion of responders and controlled patients. Both drugs were well tolerated but a greater percentage of those in the lisinopril group (80% vs 69%) had a least one side effect (*P*=0.020). The proportion of patients spontaneously reporting cough (23.1% vs 4.6%) and discontinuing therapy due to adverse events (12.0% vs 5.9%) was also higher in the lisinopril group compared with the candesartan group.
Ohma et al[23] Candesartan 16 mg and HCTZ 12.5 mg once daily vs losartan 50 mg and HCTZ 12.5 mg once daily	DB, MC, RCT Patients aged 20-80 years with mild-to-moderate uncontrolled hypertension while on monotherapy (any kind of medication)	N=340 12 weeks	Primary: Change in sitting DBP Secondary: SBP, proportion of responders, safety and tolerability	Primary: Greater reductions in DBP were reported with candesartan and HCTZ vs losartan and HCTZ (–10.4 vs –7.8 mm Hg; *P*=0.016). Secondary: Greater decreases in SBP were reported with candesartan and HCTZ (–19.4 mm Hg) vs losartan and HCTZ (–13.7 mm Hg; *P*=0.004). The proportion of patients achieving a DBP ≤90 mm Hg was greater with candesartan and HCTZ (60.9% vs 49.3%; *P*=0.044). There were 8 withdrawals due to adverse effects in the candesartan and HCTZ group and 12 in the losartan and HCTZ group. The most common adverse effects were headache,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				tachycardia/palpitations, dizziness, and fatigue.
Neutel, Franklin, Oparil et al[24] Irbesartan 150 mg for 1 week with forced titration to 300 mg monotherapy for 6 weeks vs irbesartan 150 mg and HCTZ 12.5 mg (fixed-dose) for 1 week then forced titration to irbesartan 300 mg and HCTZ 25 mg for 6 weeks	AC, DB, MC, PRO, RCT Patients ≥18 years with severe hypertension who were untreated (seated DBP ≥110 mm Hg) or currently receiving antihypertensive monotherapy with DBP ≥100 mm Hg	N=737 7 weeks	Primary: Proportion of patients with DBP <90 mm Hg at week 5 Secondary: Proportion of patients who achieved seated SBP/DBP <140/90 mm Hg	Primary: Significantly more patients on combination therapy achieved seated DBP <90 mm Hg at week 5 compared with monotherapy (47.2% vs 33.2%; *P*=0.0005). Secondary: Significantly more patients attained SBP/DBP <140/90 mm Hg at week 5 (34.6% vs 19.2%, respectively; *P*<0.0001), while the mean difference between combination and monotherapy in seated DBP and SBP was 4.7 and 9.7 mm Hg, respectively (*P*<0.0001). Greater and more rapid blood pressure reduction with irbesartan plus HCTZ was achieved without additional side effects.
Neutel, Franklin, Lapuerta et al[25] Irbesartan 300 mg and HCTZ 25 mg QD vs irbesartan 300 mg QD vs HCTZ 25 mg QD	AC, DB, PG, PRO, RCT Patients (mean age 55 years) with moderate hypertension (seated SBP 160-179 mm Hg when DBP <110 mm Hg; or DBP 100-109 mm Hg when SBP <180 mm Hg)	N=538 (with a 3:1:1 randomization) 12 weeks	Primary: Change in SBP after week 8 Secondary: Change from baseline in DBP at weeks 8 and 12, SBP at week 12, proportion of responders (SBP <140 mm Hg and DBP <90 m Hg) at weeks 8 and 12	Primary: At week 8, there was a reduction in SBP of 27.1 mm Hg with irbesartan and HCTZ compared to 22.1 mm Hg with irbesartan monotherapy (*P*=0.0016) and 15.7 mm Hg with HCTZ (*P*<0.0001). Secondary: At week 8, there was a reduction in DBP of 14.6 mm Hg with irbesartan and HCTZ compared to 11.6 mm Hg with irbesartan monotherapy (*P*=0.0013) and 7.3 mm Hg with HCTZ (*P*<0.0001). A significantly greater percentage of patients reached a treatment goal of SBP <140 mm Hg and DBP <90 mm Hg by week 8 with irbesartan and HCTZ (53.4%) compared with irbesartan (40.6%; *P*=0.0254) and HCTZ (20.2%; *P*<0.0001) alone. Treatment was well tolerated in all 3 treatment groups with a slight increase in adverse events in the combination therapy group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Weir et al[26] Irbesartan 300 mg and HCTZ 25 mg QD (fixed-dose combination)	Post hoc pooled analysis of 2 AC, DB, MC, RCT Patients with stage 1 or 2 hypertension evaluated according to age (n=121 for ≥65 years and n=675 for <65 years), presence or absence of obesity (n=378 or n=414), type 2 diabetes (n=99 or n=697), and high World Health Organization-defined cardiovascular risk (n=593 or n=202)	N=796 7-8 weeks	Primary: Antihypertensive efficacy, tolerability Secondary: Not reported	Primary: SBP/DBP reductions (27-31/16-22 mm Hg) were similar regardless of age, obesity and type 2 diabetes status and were greater in high- vs low-risk patients. Dizziness (2.0%-3.7%), hypotension (0%-0.7%), and syncope (0%) were rare and not centered in any subgroup. There was no hypotension in the elderly or in patients with type 2 diabetes. Secondary: Not reported
Bobrie et al[27] Irbesartan 150 mg and HCTZ 12.5 mg QD vs valsartan 80 mg and HCTZ 12.5 mg QD	OL, PRO, RCT, blinded-end point Patients whose blood pressure remained uncontrolled after 5 weeks of HCTZ 12.5 mg QD	N=464 8 weeks (after 5 week lead-in with HCTZ)	Primary: Blood pressure reductions, safety Secondary: Not reported	Primary: Irbesartan and HCTZ produced greater reductions in average SBP and DBP measured by home blood pressure monitoring than valsartan and HCTZ (SBP, –13.0 vs –10.6 mm Hg; *P*=0.0094; DBP, –9.5 vs –7.4 mm Hg; *P*=0.0007). These differences were more pronounced in the morning than in the evening. Normalization rates observed with home blood pressure monitoring (SBP <135 mm Hg and DBP <85 mm Hg) were significantly greater with irbesartan and HCTZ than with valsartan and HCTZ (50.2% vs 33.2%; *P*=0.0003). The overall safety was similar in the 2 groups. Secondary: Not reported
Dahlöf et al[28] LIFE Losartan 50 to 100 mg/day	DB, DD, PG, RCT Patients 55 to 80 years old with essential hypertension (sitting	N=9,193 ≥4 years (4.8 years mean follow-up)	Primary: Composite of cardiovascular death, myocardial infarction and stroke	Primary: SBP fell by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively (treatment difference, *P*=0.017) and DBP fell by 16.6 and 16.8 mm Hg, respectively (treatment difference, *P*=0.37). Mean arterial pressure was 102.2 and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
with HCTZ 12.5 to 25 mg/day if needed for blood pressure control vs atenolol 50 to 100 mg/day, with HCTZ 12.5 to 25 mg/day if needed for blood pressure control	SBP/DBP 160-200/95-115 mm Hg) and LVH		Secondary: All-cause mortality, hospitalization for angina or heart failure, revascularization procedures, resuscitated cardiac arrest, new-onset diabetes	102.4 mm Hg, respectively (*P*=NS). Heart rate decreased more in patients assigned to atenolol than losartan (–7.7 vs –1.8 beats/minute, respectively; *P*<0.0001). Compared to atenolol, the primary composite occurred in 13.0% fewer patients receiving losartan (RR, 0.87; 95% CI, 0.77 to 0.98; *P*=0.021). While there was no difference in the incidence of cardiovascular mortality (*P*=0.206) and myocardial infarction (*P*=0.491), losartan treatment resulted in a 24.9% relative risk reduction in stroke compared to atenolol (*P*=0.001). Secondary: A 25% lower incidence of new-onset diabetes was reported with losartan compared to atenolol (*P*=0.001). There was no significant difference among the other secondary end points between the 2 treatment groups. Note: At end point or end of follow-up, 18% and 26% of patients on losartan were receiving HCTZ alone or with other drugs, respectively. In the atenolol group, 16% and 22% of patients were receiving HCTZ alone or with other drugs, respectively.
Salerno et al[29] Losartan vs losartan and HCTZ Doses were titrated as needed at 2-week intervals to reach goal blood pressure (<90 mm Hg).	DB, RCT Patients with severe hypertension	N=585 6 weeks	Primary: Proportion of patients achieving goal blood pressure Secondary: Adverse events	Primary: Almost twice as many patients achieved goal blood pressure at 4 weeks on losartan 50 mg and HCTZ 12.5 mg vs losartan 50-100 mg monotherapy (*P*=0.002). Almost 3 times as many patients achieved goal blood pressure at 6 weeks with losartan and HCTZ vs losartan monotherapy (*P*<0.001). Adverse experiences on losartan and HCTZ (43%) were significantly less than with losartan monotherapy (53%).
Minami et al[30]	OL	N=15	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Losartan 50 mg and HCTZ 12.5 mg (separate administration) vs candesartan 8 mg QD (n=10) or amlodipine 5 mg QD (n=5)	Japanese outpatients with essential hypertension treated for at least 2 months with either candesartan or amlodipine and 24-hour ambulatory blood pressure ≥135/80 mm Hg	12 months	Changes in blood pressure Secondary: Not reported	In patients who had previously received candesartan, 24-hour blood pressure decreased significantly from 137/89 mm Hg to 126/81 mm Hg after 3 months (P<0.05/P<0.001) and to 123/81 mm Hg after 12 months (P<0.01/P<0.001) of treatment with losartan and HCTZ. In patients who had previously received amlodipine, 24-hour blood pressure decreased significantly from 137/81 to 125/75 mm Hg after 3 months (P<0.05/P<0.05) and to 124/77 mm Hg after 12 months (P<0.05/P=NS) of treatment with losartan and HCTZ. There were significant decreases in SBP during the daytime, nighttime and early morning after 12 months in both groups. No adverse changes in the indices of glucose or lipid metabolism were observed in either group. Secondary: Not reported
Lacourcière et al[31] PROBE Losartan 50 mg and HCTZ 12.5 mg vs telmisartan 40 mg and HCTZ 12.5 mg vs telmisartan 80 mg and HCTZ 12.5 mg	DB, MC, OL, RCT, blinded-end point trial Patients ≥18 years of age with mild-to-moderate essential hypertension	N=597 6 weeks	Primary: Mean changes in ambulatory DBP Secondary: Mean changes in ambulatory SBP, 24-hour DBP, safety	Primary: During the last six hours of the dosing interval, telmisartan 40 mg plus HCTZ 12.5 mg and telmisartan 80 mg plus HCTZ 12.5 mg reduced mean DBP to a greater extent vs losartan 50 mg plus HCTZ 12.5 mg. Treatment differences between the groups were 1.8 mm Hg (P<0.05) and 2.5 mm Hg (P<0.001) lower, respectively, with the telmisartan and HCTZ arms. Secondary: Telmisartan 40 mg plus HCTZ 12.5 mg and telmisartan 80 mg plus HCTZ 12.5 mg produced greater reductions in ambulatory SBP vs losartan 50 mg plus HCTZ 12.5 mg of 2.5 and 3.4 mm Hg, respectively, during the last six hours of the dosing interval (P<0.05), and of 2.1 and 3.4 mm Hg, respectively, over the entire 24-hour dosing interval (P<0.05). Telmisartan 80 mg plus HCTZ 12.5 mg also lowered mean 24-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				hour DBP by 2.3 mm Hg more than losartan 50 mg plus HCTZ 12.5 mg (*P*<0.001). All treatments were well tolerated.
Oparil et al[32] Losartan 50 to 100 mg/day (±HCTZ 12.5 to 25 mg/day) vs amlodipine 5 to 10 mg/day (±HCTZ 12.5 to 25 mg/day)	DB, DD, MC, PG, RCT Patients with hypertension began monotherapy regimen, if goal DBP (≤90 mm Hg) was not attained, drug doses could be doubled and/or HCTZ mg was added	N=900 12 weeks	Primary: Efficacy, tolerability, effects on quality of life Secondary: Not reported	Primary: DBP reductions after 4, 8, and 12 weeks of therapy were clinically comparable (losartan group: 7.3, 10.4, and 11.1 mm Hg, respectively; amlodipine group: 7.9, 11.2, and 11.8 mm Hg, respectively) (*P* value not significant). Similar reductions in SBP were seen for both treatment groups (*P* value not significant). The percentage of patients reaching goal DBP (≤90 mm Hg) or DBP ≥90 mm Hg with a ≥10 mm Hg decrease from baseline) was comparable for the two groups, with 68% of patients in the losartan group and 71% of patients in the amlodipine group reaching goal. Significantly more patients in the amlodipine group had drug-related adverse experiences (27% vs 13%; *P*=0.029). Edema was more common in patients receiving the amlodipine regimen than in those receiving the losartan regimen (11% vs 1%; *P*=0.004). Overall quality of life was not different in the 2 treatment groups.
Chrysant et al[33] Olmesartan and HCTZ (all possible combinations of doses used in monotherapy) vs olmesartan monotherapy (10, 20 or 40 mg/day)	DB, RCT, factorial design Patients with a baseline mean seated DBP of 110-115 mm Hg	N=502 8 weeks	Primary: Change in DBP at week 8 Secondary: Change in SBP at week 8	Primary: Olmesartan and HCTZ produced greater reductions in seated DBP at week 8 than did monotherapy with either component. All olmesartan and HCTZ combinations significantly reduced DBP compared with placebo in a dose-dependent manner. Reductions in mean trough DBP were 8.2, 16.4 mm Hg, and 21.9 mm Hg with placebo, olmesartan 20 mg plus HCTZ 12.5 mg, and olmesartan 40 mg plus HCTZ 25 mg, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs HCTZ monotherapy (12.5 or 25 mg/day) vs placebo				Secondary: Olmesartan and HCTZ produced greater reductions in seated SBP at week 8 than did monotherapy with either component. All olmesartan and HCTZ combinations significantly reduced DBP compared with placebo in a dose-dependent manner. Reductions in mean trough SBP were 3.3, 20.1, and 26.8 mm Hg with placebo, olmesartan 20 mg plus HCTZ 12.5 mg, and olmesartan 40 mg plus HCTZ 25 mg, respectively. All treatments were well tolerated.
Kereiakes et al[34] Olmesartan 20 mg/day for 2 weeks, then 40 mg/day for 2 weeks then olmesartan/HCTZ 40/12.5 mg/day (fixed-dose combination) for 4 weeks increased to 40/25 mg for 4 weeks vs benazepril 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, then benazepril 20 mg/day plus amlodipine 5 mg/day for 4 weeks, then benazepril 20 mg/day plus amlodipine 10 mg/day for 4 weeks	DB, DD, MC, PG, RCT Patients with stage 2 hypertension (mean seated DBP ≥90 mm Hg but <115 mm Hg and SBP ≥160 mm Hg but <200 mm Hg or DBP ≥100 mm Hg but <115 mm Hg)	N=190 12 weeks	Primary: Change in mean seated SBP at the end of week 12 Secondary: DBP at the end of week 12, percent of patients attaining blood pressure goals of <140/90 mm Hg, <130/85 mm Hg, and <130/80 mm Hg	Primary: Patients treated with olmesartan/HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril/amlodipine (least square mean change, –32.5 vs –26.5 mm Hg; *P*=0.024; least square mean treatment difference, –6.0 mm Hg; 95% CI, –11.1 to –0.8 mm Hg). Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan/HCTZ compared with benazepril/amlodipine at week 12 (*P*=0.056). The percentage of patients achieving goal rates at the end of the study for olmesartan/HCTZ and benazepril/amlodipine were 66.3% and 44.7% (*P*=0.006) for <140/90 mm Hg, 44.9% vs 21.2% (*P*=0.001) for <130/85 mm Hg, and 32.6% and 14.1% (*P*=0.006) for <130/80 mm Hg. Both treatments were well tolerated.
Karlberg et al[35] TEES Telmisartan 20 to 80 mg/day	DB, DD, MC, PG, RCT Elderly patients (≥65 years) with mild-to-moderate hypertension	N=278 26 weeks	Primary: Change from baseline in supine SBP and DBP	Primary: Both treatments had similar rates of HCTZ use. Both treatments showed comparable decreases in blood pressure. Mean changes in DBP were –12.8 mm Hg for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
with add-on HCTZ 12.5 or 25 mg/day daily as needed to reach DBP goal (≤90 mm Hg) vs enalapril 5 to 20 mg/day daily, with add-on HCTZ 12.5 or 25 mg/day daily as needed to reach DBP goal (≤90 mm Hg)	received telmisartan or enalapril and HCTZ was added at week 12 if needed		Secondary: Proportion of responders, safety	telmisartan and –11.4 mm Hg for enalapril (*P*=0.074). Mean changes in SBP were –22.1 mm Hg for telmisartan and –20.1 mm Hg for enalapril (*P*=0.350). Secondary: Overall, 63% and 62% of patients responded to telmisartan and enalapril, respectively, with a DBP of <90 mm Hg. Both regimens provided effective blood pressure lowering over the 24-hour dosing interval, as determined by ambulatory blood pressure monitoring. Both regimens were well tolerated; however, the enalapril group had a higher incidence of cough than the telmisartan group (15.8% vs 6.5%; no *P* value reported).
Waeber et al[36] Valsartan 80 mg/day switched to valsartan 80 mg and HCTZ 12.5 mg/day, or combination of valsartan 80 mg and benazepril 10 mg/day	OL, RCT Patients with mild-to-moderate uncontrolled hypertension (DBP ≥90) while on valsartan monotherapy	N=327 4 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: The 2 combinations produced an additional blood pressure reduction compared to monotherapy (both *P*<0.001), with similar DBP reductions reported for the 2 combination groups (–4.5 mm Hg with valsartan plus HCTZ and –3.3 mm Hg with valsartan plus benazepril; no *P* value reported). SBP reductions of – 6.7 and –3.2 mm Hg with valsartan plus HCTZ and valsartan plus benazepril, respectively, were reported (*P*=0.1). At the end of the trial, the blood pressure of the responders to valsartan monotherapy was lower than that of patients requiring combination therapy. Valsartan given alone or in association with HCTZ or benazepril was well tolerated. Secondary: Not reported
Schweizer et al[37] Valsartan 160 mg and HCTZ	Nonrandomized, OL Hypertensive patients not	N=197 8 weeks	Primary: Reduction in mean sitting DBP between	Primary: At baseline, DBP was 103.0 mm Hg. After 4 weeks of candesartan and HCTZ, DBP decreased to 93.8 mm Hg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
25 mg (fixed-dose) QD vs candesartan 32 mg and HCTZ 25 mg (separate administration) QD	adequately controlled by free combination of candesartan and HCTZ for 4 weeks		week 4 and 8 Secondary: Reduction in mean sitting SBP between week 4 and 8	(n=197). Subsequent treatment with valsartan and HCTZ for 4 additional weeks reduced DBP to 88.7 mm Hg (n=138). This represented an additional decrease in DBP of 5.1 mm Hg (*P*<0.0001). Secondary: The valsartan and HCTZ fixed-dose combination reduced SBP by 3.4 mm Hg (*P*=0.0029).
Fogari et al[38] Valsartan 160 mg and HCTZ 12.5 mg QD vs olmesartan 20 mg and HCTZ 12.5 mg QD	PRO, PG, RCT Hypertensive patients aged 35-75 years with DBP 90-110 mm Hg after 4 weeks of monotherapy on either valsartan or olmesartan	N=130 8 weeks (4 weeks of combination therapy)	Primary: Changes in blood pressure Secondary: Not reported	Primary: Both combinations induced a greater ambulatory blood pressure reduction than monotherapy. However, mean reduction from baseline in the valsartan and HCTZ-treated patients (–21.5/–14.6 mm Hg for 24 hours, –21.8/–14.9 mm Hg for daytime, and –20.4/–13.7 mm Hg for nighttime SBP/DBP) was greater than in the olmesartan and HCTZ-treated patients (–18.8/–12.3 mm Hg for 24 hours, –19.3/–12.8 mm Hg for daytime, and –17.4/–10.6 mm Hg for nighttime SBP/DBP). The difference between the effects of the 2 treatments was significant (*P*<0.01). Plasma concentrations of HCTZ were significantly greater with valsartan than with olmesartan at each determination time (*P*<0.05). Secondary: Not reported
White et al[39] Valsartan 160 mg and HCTZ 25 mg QD vs telmisartan 80 mg and HCTZ 25 mg QD vs	DB, PC, RCT Hypertensive patients	N=1,181 8 weeks	Primary: Changes in DBP and SBP at 8 weeks Secondary: Safety	Primary: Changes from baseline in blood pressure following telmisartan and HCTZ (–24.6/–18.2 mm Hg) were significantly greater than both valsartan and HCTZ (–22.5/–17.0 mm Hg; *P*=0.017 for SBP and *P*=0.025 for DBP), and placebo (–4.1/–6.1 mm Hg; *P*<0.0001). Secondary: The total number of patients with at least 1 adverse event reported was similar among the 3 treatment groups and was 37% for valsartan and HCTZ, 36% for telmisartan and HCTZ,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo (4:4:1 randomization)				and 42% for placebo.
Sharma et al[40] SMOOTH Valsartan 160 mg for 4 weeks with add-on HCTZ 12.5 mg for 6 weeks vs telmisartan 80 mg for 4 weeks and add-on HCTZ 12.5 mg for 6 weeks	MC, PRO, OL, RCT, blinded-end point Men and women aged ≥30 years with mild-to-moderate hypertension (mean seated SBP 140-179 mm Hg and/or DBP 95-109 mm Hg), with type 2 diabetes and BMI >27 kg/m^2	N=840 10 weeks	Primary: Change in mean ambulatory SBP and DBP Secondary: Not reported	Primary: At 10 weeks, telmisartan and HCTZ provided significantly greater reductions in the last 6 hours of mean ambulatory blood pressure (differences in SBP were 3.9 mm Hg; *P*<0.0001 and differences in DBP were 2.0 mm Hg; *P*=0.0007). Telmisartan and HCTZ also produced significantly greater reductions than valsartan and HCTZ in 24-hour mean ambulatory blood pressure (differences in SBP were 3.0 mm Hg; *P*=0.0002 and differences in DBP were 1.6 mm Hg; *P*=0.0006) and during morning, daytime and nighttime periods (*P*<0.003). Both treatments were well tolerated. Secondary: Not reported
Conlin et al[41] PREVAIL Candesartan 8 to 16 mg/day, irbesartan 150 to 300 mg/day, losartan 50 to 100 mg/day, and valsartan 80 to 160 mg/day vs another ARB vs	MA of 43 PC, RCT Trials involved ARBs vs placebo, other antihypertensive classes, and direct comparisons between ARBs	N=11,281 Duration varied	Primary: Weighted average for SBP and DBP reduction with ARB monotherapy, dose titration, and with the addition of low-dose HCTZ were calculated; responder rates Secondary: Not reported	Primary: The absolute weighted-average reductions in DBP (8.2 to 8.9 mm Hg) and SBP (10.4 to 11.8 mm Hg) for ARB monotherapy were comparable for all ARBs (no *P* value reported). Responder rates for ARB monotherapy were 48% to 55%. Dose titration resulted in slightly greater blood pressure reduction and an increase in responder rates of 53% to 63% (no *P* value reported). ARB and HCTZ combinations produced substantially greater reductions in SBP (16.1 to 20.6 mm Hg) and DBP (9.9 to 13.6 mm Hg) than ARB monotherapy (no *P* value reported). Responder rates for ARB and HCTZ combinations were 56% to 70% (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ARB plus low-dose HCTZ				The authors concluded that candesartan, irbesartan, losartan and valsartan produced comparable antihypertensive efficacy when administered at their recommended doses, a near flat dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ. Secondary: Not reported

Drug regimen abbreviations: HCTZ=hydrochlorothiazide, QD=once daily
Study abbreviations: AC=active comparator, CI=confidence interval, DB=double-blind, DD=double dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ARB=angiotensin II receptor antagonist, CAD=coronary artery disease, DBP=diastolic blood pressure, LVH=left ventricular hypertrophy, NYHA=New York Heart Association, SBP=systolic blood pressure

Additional Evidence

Dose Simplification:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Combination Angiotensin II Receptor Antagonists

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
candesartan and hydrochlorothiazide	tablet	Atacand HCT®	$$$	N/A
eprosartan and hydrochlorothiazide	tablet	Teveten HCT®	$$$	N/A
irbesartan and hydrochlorothiazide	tablet	Avalide®	$$$	N/A
losartan and hydrochlorothiazide	tablet	Hyzaar®	$$$	N/A
olmesartan and hydrochlorothiazide	tablet	Benicar HCT®	$$$	N/A
telmisartan and hydrochlorothiazide	tablet	Micardis HCT®	$$$	N/A
valsartan and hydrochlorothiazide	tablet	Diovan HCT®	$$$	N/A

No generic products are available in this class.
N/A=not available.

X. Conclusions

The combination angiotensin II receptor antagonists or blockers (ARBs) combine an ARB with hydrochlorothiazide in a fixed-dose formulation. While hydrochlorothiazide is available generically, none of the single entity or combination ARBs are available generically. All of the combination ARBs are Food and Drug Administration (FDA) approved for the treatment of hypertension. The fixed-dose combination of losartan and hydrochlorothiazide is also approved to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to African American patients.[16]

According to the consensus guidelines, many people will need more than one antihypertensive medication to achieve blood pressure goals.[5,7,8,10] Most patients with stage 2 or grade II hypertension will require initial therapy with medications from 2 drug classes.[5,7,8,11] According to the Seventh Report of the Joint National Committee (JNC 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes.[5] ARBs are recommended as initial therapy for patients with hypertension and other comorbidities, such as heart failure, diabetes, and chronic kidney disease. The fixed-dose combinations of losartan and valsartan with hydrochlorothiazide have been shown to be safe and effective when administered as initial therapy for hypertension.[16,19] While the fixed-dose combination products may favor compliance and simplify regimens,[7] there are no prospective randomized head-to-head controlled trials that have demonstrated better clinical outcomes than administration of the individual components. In patients not controlled by the combination of candesartan and hydrochlorothiazide, Schweizer et al reported that the fixed-dose combination of valsartan and hydrochlorothiazide produced a statistically and clinically significant additional blood pressure reduction.[37]

Studies have shown an additive response in blood pressure lowering when ARBs are used in combination with hydrochlorothiazide.[26,28,29] There are limited direct head-to-head comparative trials of the combination ARBs. The few comparative studies available show minimal differences in blood pressure-lowering ability between the combination ARBs.[23,25] In general, these differences amount to a few mm Hg in blood pressure-lowering capacity. While the minute differences in blood pressure lowering may be statistically significant, the clinical significance has not been established. Overall, there is insufficient data to conclude that one combination ARB is safer or more efficacious than another and that administration of the fixed-dose combination results in better clinical outcomes.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand combination angiotensin II receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Mineralocorticoid (Aldosterone) Receptor Antagonists
Single Entity Agents
AHFS Class 243220
September 10, 2008

I. Overview

The agents known as aldosterone receptor antagonists or mineralocorticoid receptor antagonists competitively inhibit the binding of aldosterone to the mineralocorticoid receptor.[1-4] Aldosterone is a component of the renin-angiotensin-aldosterone (RAAS) system responsible for the regulation of extracellular volume and blood pressure. Upon binding to the mineralocorticoid receptor on the distal renal tubule, aldosterone activates the sodium-potassium exchange pump (Na+-K+ ATPase), leading to sodium/water retention and potassium excretion. By inhibiting the effects of aldosterone, aldosterone receptor antagonists may lead to diuresis as well as blood pressure reduction. Since the majority of sodium/water reabsorption takes place on the proximal renal tubule, the diuretic effect associated with this medication class is mild, unless taken in conjunction with other diuretics. The aldosterone receptor antagonists may also exert a cardioprotective effect by antagonizing aldosterone-mediated myocardial and vascular remodeling, collagen deposition, myocardial stiffness, hypokalemia, arrhythmia, and suppression of nitric oxide release.[3,4] Finally, aldosterone receptor antagonists have a role in conditions of excessive aldosterone secretion (i.e., edema, hyperaldosteronism).[2,3]

The American Hospital Formulary Service (AHFS) class of Mineralocorticoid (Aldosterone) Receptor Antagonists includes eplerenone and spironolactone as single entity agents. All agents are formulated for oral administration. Spironolactone is available generically but eplerenone is available only as a branded product. The single entity aldosterone receptor antagonists are Food and Drug Administration (FDA) approved for the treatment of hypertension.[1,2] While eplerenone is recognized as having a survival benefit for patients with congestive heart failure (CHF) sustained after an acute myocardial infarction, spironolactone is only indicated for the symptomatic management of edema and sodium retention secondary to CHF. However, results of a large clinical study suggest that spironolactone decreases overall mortality and hospitalization in patients with moderate-to-severe CHF.[3] Spironolactone is also indicated for edematous conditions secondary to cirrhosis and/or nephrotic syndrome.[1,2] Additional FDA-approved indications with spironolactone include the treatment of hypokalemia as well as diagnosis and management of primary hyperaldosteronism.

Due to their activity on the sodium/potassium pump, aldosterone receptor antagonists are also considered to be potassium-sparing diuretics.[3-4] Aldosterone receptor antagonists are associated with increases in serum potassium levels, warranting the need for potassium monitoring.[1-3] Moreover, these agents are contraindicated in patients with hyperkalemia and in the setting of significantly impaired renal function. Caution is also warranted when these agents are used concomitantly with potassium supplements and other agents that can increase potassium levels. When used for the treatment of hypertension, eplerenone is contraindicated in patients receiving concurrent potassium supplements or other potassium-sparing diuretics, in type 2 diabetic patients with microalbuminuria, or in those with creatinine clearance <50 ml/min, serum creatinine >2 mg/dL (males) or >1.8 mg/dL (females).[1] While eplerenone is a selective aldosterone receptor antagonist, spironolactone may also antagonize glucocorticoid, progesterone, and androgen receptors.[1,3,4] Consequently, spironolactone is associated with steroid-related adverse effects (eg, gynecomastia, impotence, menstrual abnormalities) that are rare with eplerenone.

The single entity mineralocorticoid (aldosterone) receptor antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
eplerenone	tablet	Inspra®	none
spironolactone	tablet	Aldactone®*	spironolactone

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the single entity mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 2. For a comprehensive overview of the pharmacologic management of acute myocardial infarction, chronic heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists[5-22]

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)[5]**	• No specific recommendation is made concerning single entity mineralocorticoid (aldosterone) receptor antagonists.
National Institute for Health and Clinical Excellence (NICE): **Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)[6]**	• Aldosterone antagonists licensed for use after a myocardial infarction (MI) should be initiated within 14 days of an MI in patients with heart failure and left ventricular systolic dysfunction, preferably after angiotensin converting enzyme (ACE) inhibitor initiation.
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)[7]**	• No specific recommendation is made concerning single entity mineralocorticoid (aldosterone) receptor antagonists.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)[8]**	Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Aldosterone antagonists may be beneficial in patients with moderately severe-to-severe symptoms of heart failure with reduced left ventricular ejection fraction, though careful monitoring is required.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)[9]**	Patients With Left Ventricular Systolic Dysfunction • An aldosterone antagonist may be added to the standard medication regimen (including diuretics) in patients who are in New York Heart Association (NYHA) functional class IV or those in class III previously in class IV (left ventricular ejection fraction ≤35%) from left ventricular systolic dysfunction. • An aldosterone antagonist should be considered in patients who have had an MI and who have symptomatic heart failure and left ventricular ejection fraction ≤40% while receiving standard therapy with an ACE inhibitor (or angiotensin receptor blocker (ARB)) and a β-adrenergic blocking agent (β-blocker). Managing Patients With Heart Failure and Hypertension • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing calcium channel blocking agent (CCB) (amlodipine) may be

Clinical Guideline	Recommendation
	considered.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)[10]**	• Potassium-sparing diuretics are only recommended if hypokalemia persists despite ACE inhibition or in patients with severe heart failure who are already on a combination of an ACE inhibitor and low-dose spironolactone, or in patients who are intolerant to even low doses of spironolactone. • Aldosterone antagonists are recommended in addition to ACE inhibitors, β-blockers, and diuretics in patients who have advanced heart failure (NYHA class III-IV) with systolic dysfunction, and in patients who are unable to tolerate therapy with ACE inhibitors. • Aldosterone antagonists are recommended in combination with an ACE inhibitor and a β-blocker in patients who have had an MI and who have left ventricular systolic dysfunction and signs of heart failure.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)[11]**	• High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should not be used in patients whose potassium levels are greater than 5.0 mEq/L.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)[12]**	• No specific recommendation is made concerning single entity mineralocorticoid (aldosterone) receptor antagonists.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)[13]**	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics).
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)[14]**	• No specific recommendation is made concerning single entity mineralocorticoid (aldosterone) receptor antagonists.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)[15]**	• No specific recommendation is made concerning single entity mineralocorticoid (aldosterone) receptor antagonists.

Clinical Guideline	Recommendation
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[16]	• No specific recommendation is made concerning single entity mineralocorticoid (aldosterone) receptor antagonists.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[17]	• No specific recommendation is made concerning single entity mineralocorticoid (aldosterone) receptor antagonists.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[18]	• No specific recommendation is made concerning single entity mineralocorticoid (aldosterone) receptor antagonists.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[19]	• ACE inhibitors and ARBs have many advantages for patients with chronic kidney disease (CKD) and associated comorbid medical conditions. They slow the progression of diabetic kidney disease and nondiabetic kidney disease with proteinuria, and in addition, they reduce proteinuria, irrespective of the type of kidney disease. • ACE inhibitors are more effective than other antihypertensive agents in slowing the progression of most nondiabetic kidney diseases. The beneficial effect is greater in patients with severe proteinuria. • ARBs may be more effective than other antihypertensive agents in slowing the progression of nondiabetic kidney disease. • ACE inhibitors and ARBs in combination may be more effective than either alone in slowing the progression of nondiabetic kidney disease. • Diuretics may potentiate the beneficial effects of ACE inhibitors and ARBs in nondiabetic kidney disease. • ACE inhibitors, ARBs, and nondihydropyridine calcium-channel blockers have a greater antiproteinuric effect than other antihypertensive classes in nondiabetic kidney disease. • Dihydropyridine calcium-channel blockers are less effective than other agents in slowing the progression of nondiabetic kidney disease with proteinuria. • The K/DOQI guidelines do not address the use of aldosterone receptor antagonists for the management of nondiabetic kidney disease.
American Association of Clinical Endocrinologists (AACE): **AACE Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Hypertension (2006)**[20]	• The following recommendations from the AACE guidelines pertain to the management of primary hyperaldosteronism: • Primary hyperaldosteronism is the cause of clinical hypertension in up to 15% cases. • Surgery is the preferred treatment modality for patients with unilateral adenomas. • The guidelines note that spironolactone may be used in lieu of surgery in female or elderly patients with small adenomas or hyperplasias. Since male patients may experience erectile dysfunction and gynecomastia with spironolactone therapy, a trial of eplerenone may be considered. • Glucocorticoid-remediable aldosteronism is treated with glucocorticoids, which suppress the adrenocorticotropic hormone (ACTH) production.
American Association for the Study of Liver Diseases (AASLD): **Management of Adult Patients with Ascites due to Cirrhosis (2004)**[21]	• A goal of treatment is to increase urinary sodium excretion to >78 mmol per day. • The guidelines recommend dietary sodium restriction (2,000 mg per day) and diuretic therapy as first line treatment in patients with ascites and cirrhosis. • Only patients who achieve urinary sodium excretion of > 78 mmol per day can bypass diuretic therapy. • The typical diuretic regimen consists of single morning doses of spironolactone, beginning with 100 mg, in addition to furosemide 40 mg. Single morning dosing improves adherence.

Clinical Guideline	Recommendation
	• Spironolactone monotherapy may be used only in patients who have minimal fluid overload. • The doses of spironolactone and furosemide may be increased every 3 to 5 days for adequate natriuresis; however, the 100/40 mg ratio should be maintained to avoid hyperkalemia. • The maximum spironolactone and furosemide daily doses are 400 and 160 mg, respectively. • In patients experiencing painful gynecomastia with spironolactone, amiloride (10 to 40 mg daily) may be an appropriate substitute. However, amiloride is more expensive and has been shown to be less effective than an active metabolite of spironolactone (potassium canrenoate) in a controlled, clinical trial. • Fluid restriction is not necessary unless serum sodium is less than 120 to 125 mmol/L. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses. • Liver transplantation should be considered in patients with cirrhosis and ascites. • Refractory ascites is defined as ascites unresponsive to sodium-restricted diet and high-dose diuretics (spironolactone 400 mg/day and furosemide 160 mg/day) • Serial therapeutic paracenteses may be performed in refractory ascites patients. • Referral for liver transplantation should be expedited in patients with refractory ascites. • Transjugular intrahepatic portasystemic stent shunt (TIPS) should be considered in appropriate patients. • Peritoneovenous shunt should be considered for patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS.
World Gastroenterology Organization (WGO) Practice Guideline. **Management of Ascites Complicating Cirrhosis in Adults**[22]	• A goal of treatment is to increase urinary sodium excretion to >78 mmol per day. • Initial oral diuretic therapy consists of single daily doses of spironolactone 100 mg, or spironolactone 100 mg in addition to furosemide 40 mg. • If used as monotherapy, spironolactone dose may be increased up to 400 mg daily. If used in combination with furosemide, the dose of both agents may be increased while maintaining the 2/5 ratio. • The maximum daily doses of spironolactone and furosemide are 400 and 160 mg, respectively. • Spironolactone monotherapy is more effective compared to furosemide monotherapy. However its use should be restricted to patients exhibiting minimal fluid overload. • Spironolactone monotherapy may be complicated by hyperkalemia and gynecomastia. Amiloride and triamterene are substitutes for spironolactone. • Indications of diuretic resistance include minimal to no weight loss and urinary sodium excretion of <78 mmol/day. Diuretic therapy should be discontinued in patients who develop encephalopathy, clinically significant complications of diuretics, hyperkalemia, metabolic acidosis with spironolactone, and whose serum sodium is <120 mmol/L or serum creatinine >2 mg/dL. • Serial large-volume paracenteses are safe and effective in patients with refractory ascites. Other potential treatment options for diuretic-refractory ascites are TIPS, peritoneovenous shunt, and liver transplantation.

III. Indications

Food and Drug Administration (FDA)-approved indications for the single entity mineralocorticoid (aldosterone) receptor antagonists 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 Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists[1,2]

Indication	Eplerenone	Spironolactone
Cardiovascular Disease:		
Congestive heart failure	✔ (post-myocardial infarction)	
Hypertension	✔ *	✔ †
Primary Hyperaldosteronism;		
Establishing the diagnosis by therapeutic trial		✔
Short-term preoperative treatment		✔
Long-term maintenance therapy		✔ ‡, §
Edematous Conditions, For Patients With:		
Congestive heart failure		✔ ‖
Liver cirrhosis with edema and/or ascites		✔ ¶ (maintenance therapy)
Nephrotic syndrome		✔ #
Hypokalemia:		
Treatment		✔ **
Prophylaxis in patients receiving digitalis		✔ **

*May be used alone or in combination with other antihypertensive agents.
†For patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate; usually in combination with other drugs.
‡In patients with discrete aldosterone-producing adrenal adenomas who are judged to be poor operative risks or who decline surgery.
§In patients with bilateral micro- or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism).
‖For the management of edema and sodium retention when the patient is only partially responsive to, or is intolerant of other therapies; also indicated for patients receiving digitalis, when other therapies are inappropriate.
¶Aldosterone levels may be high in this condition. In addition to pharmacotherapy, fluid and sodium intake should be restricted.
May be used when treatment of the underlying condition, fluid and sodium intake restriction, as well as the use of other diuretics do not provide adequate response.
**When other measures are considered inadequate or inappropriate.

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists[1,2,4,23,24]

Drug(s)	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Eplerenone	69	50	Hepatic, CYP3A4	None	Urine (67) Feces (32)	4-6
Spironolactone	~73*	>90	Hepatic, renal	Yes, canrenone, 7-α-thiomethyl-spironolactone, 6-β-hydroxy-7-α-thiomethylspironolactone	Urine (47-57) Feces (35-41)	1.3-1.4

* Food increases the absorption of spironolactone by almost 100%. However the clinical implication of this effect is unknown.

V. Drug Interactions

Significant drug interactions with the single entity mineralocorticoid (aldosterone) receptor antagonists are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists[25]

Drug(s)	Significance Level	Interaction	Mechanism

Drug(s)	Significance Level	Interaction	Mechanism
Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	1	Angiotensin-converting enzyme (ACE) inhibitors (all)	ACE inhibitors in combination with potassium-sparing diuretics may increase serum potassium concentrations in certain high-risk (i.e., renally impaired) patients via an unknown mechanism. Adjust dose as necessary; monitor patients' renal function and serum potassium levels.
Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	1	Angiotensin II receptor antagonists (ARBs) (all)	ARBs in combination with potassium-sparing diuretics may increase serum potassium concentrations in certain high-risk (i.e., renal impairment, type 2 diabetes) patients, via an unknown mechanism, leading to additive or synergistic effects. Adjust dose as necessary; monitor patients' renal function and serum potassium levels.
Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	1	Potassium supplements (potassium acetate, potassium acid phosphate, potassium bicarbonate, potassium chloride, potassium citrate, potassium gluconate, potassium iodide, potassium phosphate)	Coadministration of potassium supplements with potassium-sparing diuretics may result in increased potassium serum concentrations and consequently an increased risk of severe hyperkalemia. This combination should not be used without documented evidence of hypokalemia unresponsive to either agent alone. If the combination is required, closely monitor serum potassium concentrations.
Eplerenone	1	Azole antifungals (itraconazole, ketoconazole)	Certain azole antifungal agents may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone. Coadministration of eplerenone with itraconazole or ketaconazole is contraindicated.
Eplerenone	1	Clarithromycin	Clarithromycin may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone. Coadministration of eplerenone with clarithromycin is contraindicated.
Eplerenone	1	Nefazodone	Nefazodone may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone. Coadministration of eplerenone with nefazodone is contraindicated.
Eplerenone	1	Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	Potassium-sparing diuretics will increase potassium retention, which may increase the risk of hyperkalemia and associated serious, potentially fatal arrhythmias. The reduced renal elimination of potassium ions by potassium-sparing diuretics is additive with the eplerenone-associated hyperkalemia. Coadministration of eplerenone with potassium-sparing diuretics is contraindicated.
Eplerenone	1	Potassium supplements (potassium acetate,	Coadministration of potassium supplements with eplerenone may result in increased potassium serum concentrations and consequently lead to an increased risk of hyperkalemia as

Drug(s)	Significance Level	Interaction	Mechanism
		potassium acid phosphate, potassium bicarbonate, potassium chloride, potassium citrate, potassium gluconate, potassium iodide, potassium phosphate)	well as associated serious, potentially fatal arrhythmias. Coadministration of eplerenone with potassium supplements is contraindicated.
Eplerenone	1	Protease inhibitors (nelfinavir, ritonavir)	Certain protease inhibitors may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone. Coadministration of eplerenone with nelfinavir or ritonavir is contraindicated.
Spironolactone	2	Digoxin	Spironolactone may decrease the positive inotropic effect of digoxin via its own negative inotropic effect. Spironolactone interferes with the tubular secretion of digoxin, leading to decreased clearance and increased digoxin plasma concentration. Adjust digoxin dose as necessary; monitor patients closely.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

Single entity mineralocorticoid (aldosterone) receptor antagonists may cause a transient elevation of blood urea nitrogen, elevation of potassium level, and other electrolyte disturbances.[1-4] Serum potassium should be obtained in patients initiating therapy with an aldosterone receptor antagonist and monitored periodically during continued use. If hyperkalemia develops, the medication should be discontinued. In addition, spironolactone has been associated with steroidal adverse events, such as gynecomastia in men, sexual dysfunction, and menstrual irregularity in women. The most common adverse reactions reported with the single entity mineralocorticoid (aldosterone) receptor antagonists are noted in Table 6.

In addition spironolactone has been shown to be a tumorigenic in chronic toxicity studies in rats. This has resulted in the black box warning outlined in Table7.

Table 6. Adverse Drug Events (%) Reported with the Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists [1,2,4,23,24]

Adverse Event	Eplerenone	Spironolactone
Cardiovascular		
Angina pectoris	✔	-
Edema	-	2
Myocardial infarction	✔	-
Central Nervous System		
Ataxia	-	✔
Dizziness	3	-
Drowsiness	-	✔
Fatigue	2	✔
Fever	-	✔
Headache	✔	✔
Lethargy	-	✔
Mental confusion	-	✔

Adverse Event	Eplerenone	Spironolactone
Dermatological		
Angioneurotic edema	✔	-
Rash	✔	✔
Endocrine and Metabolic		
Amenorrhea	-	✔
Breast carcinoma	-	✔
Deepening of the voice	-	✔
Gynecomastia	≤ 1	≤ 52.2
Hirsutism	-	✔
Hyperchloremic metabolic acidosis	-	✔
Hypercholesterolemia	≤ 1	-
Hyperkalemia	≤ 32	≤ 40
Hypertriglyceridemia	15	-
Hyponatremia	2.3	✔
Irregular menses	-	✔
Mastodynia	≤ 1.3	2
Postmenopausal bleeding	-	✔
Gastrointestinal		
Abdominal pain	1	-
Cholestatic toxicity	-	✔
Cramping	-	✔
Diarrhea	2	✔
Gastritic bleeding	-	✔
Nausea	-	✔
Ulceration	-	✔
Vomiting	-	✔
Genitourinary		
Albuminuria	1	-
Erectile dysfunction	-	✔
Renal dysfunction	-	✔
Renal failure	-	✔
Vaginal bleeding, abnormal	≤ 2.1	-
Hematologic		
Agranulocytosis	-	✔
Eosinophilia	-	✔
Thrombocytopenia	-	✔
Laboratory Test Abnormalities		
Alanine aminotransferase increased	✔	-
Blood urea nitrogen increased	0.5	✔
Creatinine increased	2.4	-
Decreased sodium	2.3	✔
Gamma glutamyl transferase increase	✔	-
Increased potassium	≤ 32	✔
Uric acid elevation	0.3	-
Respiratory		
Cough	2	-
Other		
Anaphylaxis	-	✔
Flu-like symptoms	2	-
Urticaria	-	✔
Vasculitis	-	✔

✔ Percent not specified.
-Event not reported or incidence <1%.

Table 7. Black Box Warning for Spironolactone[2,25]

Warning
Spironolactone has been shown to be a tumorigenic in chronic toxicity studies in rats. Spironolactone should be used only in those conditions for which it is indicated. Unnecessary use of this drug should be avoided.

VII. Dosing and Administration

The usual dosing regimens for the single entity mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 8.

Table 8. Usual Dosing for the Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists [1-2,4]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Eplerenone*†	Congestive heart failure post-myocardial infarction: Initial, 25 mg once daily for 4 weeks; maintenance, 50 mg once daily Hypertension: ‡, § Initial, 50 mg once daily; maximum, 50 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg
Spironolactone	Primary hyperaldosteronism-establishing the diagnosis by a therapeutic trial: (Long test): 400 mg daily for 3 to 4 weeks (Short test): 400 mg daily for 4 days Primary hyperaldosteronism-short-term preoperative therapy: 100 to 400 mg daily prior to surgery Primary hyperaldosteronism-long-term maintenance therapy: Initial, 100 to 400 mg daily; maintenance, minimally effective doses; maximum, 400 mg daily Edematous condition (congestive heart failure, hepatic cirrhosis, or nephrotic syndrome): ‖ Initial, 100 mg once daily in single or divided doses for ≥5 days; maintenance, 25 to 200 mg once daily; maximum, 400 mg daily Essential hypertension: ‖ Initial, 50 to 100 mg once daily in single or divided doses for ≥2 weeks; maintenance, 25 to 200 mg once daily; maximum, 400 mg daily Hypokalemia: 25 to 100 mg once daily	Safety and efficacy in children have not been established.	Capsule: 25 mg 50 mg 100 mg

*Dose should be adjusted based on the patient's serum potassium level.
† Dose adjustment is not necessary in elderly or patients with mild-to-moderate hepatic impairment.
‡ Doses above 100 mg/day are not recommended since they are associated with an increased risk of hyperkalemia without an additional effect on blood pressure.
§ For hypertensive patients on concomitant moderate CYP3A4 inhibitors (eg, erythromycin, saquinavir, verapamil, fluconazole), the initial dose should be reduced to 25 mg once daily.
‖For greater efficacy, may add a second diuretic acting on the proximal renal tubule.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists[25-49]

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Congestive Heart Failure				
Pitt et al[26] 4E-Left Ventricular Hypertrophy Study Eplerenone 200 mg tablet in addition to placebo capsule once daily vs enalapril 40 mg capsule in addition to placebo tablet once daily vs eplerenone 200 mg tablet in addition to enalapril 10 mg capsule once daily If the blood pressure was uncontrolled on study medication at week-8, open label HCTZ 12.5 to 25 mg daily and/or amlodipine 10 mg daily were allowed.	AC, DB, PG, RCT Male and nonpregnant women, 58.7 years of age on average, with left ventricular hypertrophy, a history of hypertension and predominantly in sinus rhythm; patients were excluded if they had orthostatic hypotension, serum potassium level <3.0 or >5.0 mEq/L, serum creatinine level >1.5 mg/dL (men) and >1.3 mg/dL (women), left ventricular ejection fraction <40%, congestive heart failure NYHA Class III-IV, unstable angina, Q-wave myocardial infarction, stroke, transient ischemic attack, percutaneous transluminal coronary angioplasty, CABG, secondary hypertension, uncontrolled type 2	N=153 9 months	Primary: Change in left ventricular mass as assessed by MRI Secondary: Reduction in SBP, DBP, response rate (DBP <90 mm Hg), change in UACR	Primary: Both treatment groups were associated with a significant reduction in left ventricular mass from baseline (*P*<0.001). The difference in left ventricular mass reduction from baseline between the two treatment groups was not statistically significant (*P*=0.258). While eplerenone/enalapril combination therapy group demonstrated significantly greater reduction in left ventricular mass from baseline compared to eplerenone monotherapy group (*P*=0.007), the effect was not statistically different from that observed in the enalapril monotherapy group (*P*=0.107). Secondary: The SBP was reduced significantly more with the eplerenone/enalapril combination group than with eplerenone alone (*P*=0.048). The other treatment groups exhibited statistically comparable reductions from baseline in mean SBP and DBP (*P* value not reported). While 70.0% of eplerenone-treated patients responded to therapy, the response rate in the enalapril monotherapy group was only 40.7% (*P*=0.003). In addition, while 79.6% of eplerenone/enalapril-treated patients responded to therapy, the response rate in the enalapril monotherapy group was only 40.7% (*P*=0.001). Combination therapy was associated with a significant reduction in UACR compared to either eplerenone or enalapril monotherapy groups (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	diabetes, hepatic or renal disease, drug or alcohol abuse problems			Adverse events were reported with similar incidence among all treatment groups (*P* value not reported). Cough was significant in enalapril patients vs eplerenone patients (*P*=0.033). Two cases of gynecomastia were reported (one with eplerenone and one with eplerenone and enalapril). Four patients (three on enalapril and one on eplerenone and enalapril) experienced impotence during the study. Seven eplerenone, two enalapril, and three eplerenone/enalapril patients experienced serious hyperkalemia (≥6.0 mmol/L).
Pitt, Remme et al[27] EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	DB, I, MC, RCT Patients, 64 years of age on average, with acute myocardial infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure); patients were excluded if they used potassium-sparing diuretics, had a serum creatinine >2.5 mg/dL or a serum potassium >5.0 mmol/L	N=6,632 mean 16 months follow-up	Primary: Death from any cause, composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event (including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia) Secondary: Death from any cause or any hospitalization, death from cardiovascular causes, any hospitalization, hospitalization for cardiovascular causes, hospitalization for heart failure, adverse events	Primary: Significantly less patients in the eplerenone group died from any cause compared to those receiving placebo (478 vs 554; RR, 0.85; 95% CI, 0.75 to 0.96; *P*=0.008). Significantly fewer patients in the eplerenone group died from or required hospitalization for cardiovascular events compared to those receiving placebo (885 vs 993; RR, 0.87; 95% CI, 0.79 to 0.95; *P*=0.002). Secondary: Significantly fewer patients in the eplerenone group died from any cause or required hospitalization compared to those receiving placebo (1,730 vs 1,829; RR, 0.92; 95% CI, 0.86 to 0.98; *P*=0.02). Death from cardiovascular causes was 12.3% in the eplerenone group and 14.6% in the placebo group (RR, 0.83; 95% CI, 0.72 to 0.94; *P*=0.005.) Fewer patients in the eplerenone group required hospitalization compared to those receiving placebo (1,493 vs 1,526; RR, 0.95; 95% CI, 0.89 to 1.02; *P*=0.2); however the difference was not statistically significant. Fewer patients in the eplerenone group required hospitalization due to a cardiovascular event compared to those receiving placebo (606 vs 649; RR, 0.91; 95% CI, 0.81 to 1.01; *P*=0.09); however the difference was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was a relative reduction of 15% in the risk of hospitalization for heart failure in the eplerenone group (RR, 0.85; *P*=0.03) and 23% fewer episodes of hospitalization for heart failure were reported in the eplerenone group compared to the placebo group (RR, 0.77; *P*=0.002). Serious hyperkalemia (serum potassium ≥6.0 mmol/L) occurred in 5.5% of the eplerenone-treated patients compared to 3.9% of patients in the placebo group (*P*=0.002). The incidence of hyperkalemia was higher among those with a lower baseline creatinine clearance (*P*<0.001). At one year, the serum creatinine concentration had increased by 0.02 mg/dL in the placebo group and by 0.06 mg/dL in the eplerenone group (*P*<0.001). There were no significant differences between eplerenone and placebo in the incidence of sex hormone-related adverse events, including gynecomastia, impotence, breast pain, and abnormal vaginal bleeding (*P*>0.05).
Pitt, White et al[28] EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary	SA Sub-analysis of the EPHESUS study, designed to evaluate effects of eplerenone after 30 days of therapy Patients, 64 years of age on average, with acute myocardial infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart	N=6,632 30 days post randomization	Primary: Death from any cause, and composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event at 30 days Secondary: Death from cardiovascular causes, sudden cardiac death, fatal or nonfatal heart failure hospitalization, adverse events	Primary: A significantly lower percentage of patients in the eplerenone group died from any cause compared to those receiving placebo (3.2% vs 4.6%; *P*=0.004). A lower percentage of patients in the eplerenone group died from or required hospitalization for cardiovascular events compared to those receiving placebo (8.6% vs 9.9%; *P*=0.074); however, the difference was not statistically significant. Secondary: A significantly lower percentage of patients in the eplerenone group died from cardiovascular cause compared to those receiving placebo (3.0% vs 4.4%; *P*=0.003). A lower incidence of sudden cardiac death was noted among patients in the eplerenone group compared to those receiving placebo (0.9%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
reperfusion therapy)	failure); patients were excluded if they used potassium-sparing diuretics, had a serum creatinine >2.5 mg/dL or a serum potassium >5.0 mmol/L			vs 1.4%; *P*=0.051); however, the difference was not statistically significant. A lower percentage of patients in the eplerenone group required hospitalization for fatal/nonfatal heart failure compared to those receiving placebo (3.4% vs 4.2%; *P*=0.106); however, the difference was not statistically significant. There was no statistically significant difference between eplerenone and placebo in the number of patients experiencing at least 1 adverse event during 30-day therapy (*P*=0.29). At 30 days, the serum potassium concentration had increased by 0.17 mmol/L in the placebo group and by 0.24 mmol/L in the eplerenone group (*P*<0.001).
Pitt, Gheorghiade, et al[29] EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	SA Sub-analysis of the EPHESUS study, designed to evaluate effects of eplerenone in patients with left ventricular ejection fraction ≤30%. Patients, 64 years of age on average, with acute myocardial infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure); patients were excluded if they used potassium-sparing	N=2,106 16 months	Primary: Death from any cause, and composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event Secondary: Death from cardiovascular causes, sudden cardiac death, a composite endpoint of heart failure death and heart failure hospitalizations	Primary: Eplerenone was associated with a significant 21% reduction in the risk of all-cause mortality compared to placebo (*P*=0.012). Eplerenone was associated with a significant reduction in the risk of the composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event compared to placebo (*P*=0.001). Secondary: Eplerenone was associated with a significant 23% reduction in the risk of cardiovascular mortality compared to placebo (*P*=0.008). The relative risk of sudden cardiac death was reduced by 33% (*P*=0.01) and heart failure mortality/heart failure hospitalization composite endpoint was reduced by 25% (*P*=0.005) with eplerenone compared with placebo. At 30 days, eplerenone was associated with relative risk reductions of 43% for all-cause mortality (*P*=0.002), 29% for cardiovascular mortality/cardiovascular hospitalization composite endpoint (*P*=0.006), and 58% for sudden cardiac death (*P*=0.008).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	diuretics, had a serum creatinine >2.5 mg/dL or a serum potassium >5.0 mmol/L			
O'Keefe, Abuisssa, et al[30] EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	SA Sub-analysis of the EPHESUS study, designed to evaluate effects of eplerenone in patients with diabetes. Patients, 66 years of age on average, with acute myocardial infarction, diabetes, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure); patients were excluded if they used potassium-sparing diuretics, had a serum creatinine >2.5 mg/dL or a serum potassium >5.0 mmol/L	N=1,483 16 months	Primary: Death from any cause, and composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event Secondary: Death from cardiovascular causes, sudden cardiac death, hyperkalemia	Primary: Eplerenone was not associated with a significant reduction in the risk of all-cause mortality compared to placebo (*P*=0.131). Eplerenone treatment in diabetic patients was associated with a significant 17% reduction in the risk of death from cardiovascular causes or hospitalization for a cardiovascular event compared to placebo (*P*=0.031). Secondary: Eplerenone was not associated with a significant reduction in the risk of cardiovascular mortality compared to placebo (*P*=0.128). Eplerenone was not associated with a significant reduction in the risk of sudden cardiac death compared to placebo (*P*=0.533). Eplerenone was associated with a greater incidence of hyperkalemia compared to placebo (5.6% vs 3%; *P*=0.015).
Pitt, Zannad et al[31] RALES Spironolactone 25 mg once daily; in the absence of hyperkalemia, the dose could be increased to 50 mg daily after 8 weeks; if	DB, I, MC, RCT Patients, 65 years of age on average, with NYHA class IV heart failure within six months and in NYHA class III-IV at study onset, diagnosed with	N=1,663 mean 24 months of follow-up	Primary: Death from any cause Secondary: Death from cardiac causes, hospitalization for cardiac causes, the combined incidence of death or hospitalization	Primary: There were 386 deaths from any cause with placebo and 284 deaths with spironolactone (RR, 0.70; 95% CI, 0.60 to 0.82; *P*<0.001). Secondary: There were 314 deaths in the placebo group and 226 deaths in the spironolactone group that were attributed to cardiac causes (RR, 0.69; 95% CI, 0.58 to 0.82; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hyperkalemia developed the dose could be decreased to 25 mg every other day vs placebo once daily	congestive heart failure ≥6 weeks, treated with an ACE inhibitor and a loop diuretic, with a left ventricular EF ≤35%; patients were excluded if they were taking potassium-sparing diuretics, had primary operable valvular heart disease, congenital heart disease, unstable angina, primary hepatic failure, active cancer, or any other life-threatening disease, a history of heart transplantation, serum creatinine >2.5 mg/dL or a serum potassium level >5.0 mmol/L		for cardiac causes, combined end point of death or hospitalizations from any cause, combined end point of death from any cause or hospitalizations from cardiac causes, change in the NYHA class, adverse events	There were 753 hospitalizations for cardiac causes in the placebo group and 515 in the spironolactone group (RR, 0.70; 95% CI, 0.59 to 0.82; *P*<0.001). The combined end point of death from cardiac causes or hospitalizations from cardiac causes showed a 32% reduction in risk among patients in the spironolactone group as compared with those in the placebo group (RR, 0.68; 95% CI, 0.59 to 0.78; *P*<0.001). The combined end point of death or hospitalizations from any cause showed a 23% reduction in risk among patients in the spironolactone group as compared with those in the placebo group (RR, 0.77; 95% CI, 0.68 to 0.86; *P*<0.001). The combined end point of death from any cause or hospitalizations from cardiac causes showed a 32% reduction in risk among patients in the spironolactone group as compared with those in the placebo group (RR, 0.68; 95% CI, 0.60 to 0.77; *P*<0.001). A significantly greater percentage of patients receiving spironolactone experienced improvement in the NYHA class compared to patients receiving placebo (41% vs 33%; *P*<0.001). Gynecomastia or breast pain was reported in 10% of men receiving spironolactone as compared to 1% of men in the placebo group (*P*<0.001). Incidence of hyperkalemia was minimal in both groups.
Chan et al[32] Spironolactone 25 mg daily in addition to candesartan 8 mg (combination group) vs candesartan 8 mg in addition to placebo (control group)	DB, PC, RCT Patients, average age 63.2 years, with LVEF <40% on ACE inhibitors >6 months; patients were excluded if they had significant valvular heart disease, congenital heart disease, any life-	N=48 1 year	Primary: Change in LVEF, left ventricular end-diastolic volume index, end-systolic volume index, left ventricular mass index, SBP, quality of life Secondary: Not reported	Primary: At 1 year, combination therapy was associated with a significant improvement in LVEF from baseline (*P*<0.01). At 1 year, combination therapy was associated with a significant reduction in left ventricular end-diastolic volume index from baseline (*P*<0.001). At 1 year, combination therapy was associated with a significant reduction in end-systolic volume index from baseline (*P*<0.0005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	threatening disease with limited life expectancy, creatinine concentration >200 µmol/L, potassium level >5 mmol/L			At 1 year, combination therapy was associated with a significant reduction in left ventricular mass index from baseline (*P*=0.002). At 1 year, combination therapy was associated with a significant reduction in SBP from baseline (*P*<0.05). The control group was not associated with significant improvements in any of the above primary outcome measures (*P* value not reported). The quality of life score improved in both study groups (*P* value not reported). Secondary: Not reported
Hyperaldosteronism				
Karagiannis et al[33] Eplerenone 25 mg twice daily, titrated up to 200 mg daily if blood pressure remained ≥140/90 mm Hg vs spironolactone 25 mg twice daily, titrated up to 400 mg daily if blood pressure remained ≥140/90 mm Hg HCTZ 12.5 mg was added to the study regimen if blood pressure remained uncontrolled at week-16.	OL, PRO, R Patients with bilateral hyperaldosteronism	N=34 16 weeks	Primary: Percentage of patients whose blood pressure <140/90 mm Hg at week-16 Secondary: Adverse events	Primary: At 16 weeks, 76.5% and 82.4% of patients randomized to receive spironolactone and eplerenone therapies, respectively, exhibited reductions in blood pressure to <140/90 mm (*P*=1.00). Secondary: Serum potassium levels were normalized in all study groups at 4 weeks of therapy (*P* value not reported). Mild hyperkalemia was noted in two patients receiving spironolactone 400 mg and in three patients on eplerenone 150 mg therapy. Two patients receiving spironolactone reported bilateral gynecomastia at week-16 (*P* value not reported). Switching from spironolactone 400 mg to eplerenone 150 mg daily was effective in resolving gynecomastia symptoms without disrupting blood pressure control.
Hypertension				
Flack et al[34]	DB, MC, PG, RCT	N=551	Primary: Mean change from	Primary: At 16 weeks, patients randomized to eplerenone exhibited

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Eplerenone 50 mg daily vs losartan 50 mg daily vs placebo once daily Doses were increased if blood pressure remained uncontrolled	Men and women ≥18 years old, with mild-to-moderate hypertension, with SBP <180 mm Hg and DBP 95 to 109 mm Hg (off medication) or if patients were receiving antihypertensive therapy their blood pressure was <140/90 mm Hg; patients were excluded if they had known secondary hypertension, insulin-dependent diabetes, hepatic disease, elevated serum creatinine level, evidence of alcohol or drug abuse, need for other antihypertensives, regular use of corticosteroids, heart failure NYHA II-IV, myocardial infarction, coronary revascularization, stroke, or transient ischemic attack within the past six months, current unstable angina, or any other serious medical condition	16 weeks	baseline in DBP at 16 weeks Secondary: Mean change from baseline at 16 weeks in SBP, SBP and DBP within and between racial groups, response rate (defined as the percentage of patients with DBP <90 mmHg or DBP ≥90 mmHg but ≥10 mmHg below baseline), urinary albumin/creatinine ratio, effect of eplerenone in patients with various baseline renin and aldosterone levels, adverse effects	significantly greater mean changes in DBP from baseline compared to either losartan- or placebo-treated groups (*P*<0.001). Secondary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in SBP from baseline compared to either losartan- or placebo-treated groups (*P*<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated African American patients (*P*<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the losartan-treated African American patients (*P*≤0.001). At 16 weeks, white patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated white patients (*P*=0.001). However, the difference in SBP- and DBP-lowering effects was not significant different between the eplerenone ad losartan groups (*P*=0.126, *P*=0.068, respectively). Significantly greater percentage of patients randomized to eplerenone exhibited a positive response to therapy compared to either placebo (64.5% vs 41.2%; *P*<0.001) or losartan group (64.5% vs 48.3%; *P*=0.003). The eplerenone group (regardless of race) exhibited statistically significant improvement in urinary albumin/creatinine ratio from baseline compared to placebo (*P*=0.003). However, the difference in urinary albumin/creatinine ratio change from baseline was not significantly different between the eplerenone and losartan groups (*P*=0.652).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to losartan, eplerenone was more effective in lowering SBP and DBP in patients with low-moderate baseline renin levels (*P*<0.05). However, the difference was not statistically significant in patients with high baseline renin levels (*P* value not reported). Compared to losartan, eplerenone was more effective in lowering SBP in patients with low or high baseline aldosterone levels (*P*<0.05). However, the difference was not statistically significant in patients with moderate baseline aldosterone levels (*P* value not reported). Compared to losartan, eplerenone was more effective in lowering DBP in patients with low baseline aldosterone levels (*P*<0.05). However, the difference was not statistically significant in patients with moderate-high baseline aldosterone levels (*P* value not reported). There were no significant differences in the incidence of adverse events noted in eplerenone, placebo or losartan groups (*P* value not reported). The reported incidence of gynecomastia, breast pain, menstrual abnormalities, impotence, hyperkalemia and decreased libido with eplerenone was low and comparable to losartan and placebo.
Hollenberg et al[35] Eplerenone 50 mg daily, titrated to a maximum of 200 mg daily to achieve a SBP below 140 mm Hg vs amlodipine 2.5 mg daily, titrated to a maximum of 10 mg/day to achieve a SBP below 140 mm Hg	RCT Patients ≥50 years of age, with untreated SBP between 140 to 190 mm Hg	N=269 24 weeks	Primary: Change in SBP and DBP, discontinuation rate, symptom distress index, SF-36 Health Survey Secondary: Not reported	Primary: Both treatment groups exhibited similar reduction in SBP and DBP from baseline (*P*=0.01). The dropout rate was 50% greater in the amlodipine group compared to the eplerenone group (*P* value not reported). Symptom distress (technique used to assess the influence of drug treatment on quality of life) index was assessed and results favored eplerenone vs. amlodipine (*P*=0.03). SF-36 Health Survey showed no significant difference between the two treatments (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both treatment groups experienced similar incidences of adverse effects (*P* value not reported). Eplerenone-treated patients did not develop breast pain/tenderness, breast enlargement, change in menstruation, gynecomastia, or loss of libido. Secondary: Not reported
Krum et al[36] Eplerenone 50 to 100 mg daily in addition to background ACE inhibitor or ARB monotherapy vs placebo once daily in addition to background ACE inhibitor or ARB monotherapy	DB, MC, PG, RCT Male or nonpregnant female patients between 18 and 85 years of age taking an ACE inhibitor or an ARB for mild-moderate hypertension (DBP ≥95 but <110 mm Hg and SBP <180 mm Hg), with potassium >3.0 mEq/L but ≤5.0 mEq/L	N=341 8 weeks	Primary: Mean change from baseline in trough cuff seated DBP and SBP at week-8 Secondary: The percentage of responders (defined as patients who had a DBP<90 mm Hg or exhibited ≥10 mm Hg reduction from baseline), adverse events	Primary: Eplerenone-treated patients exhibited a statistically significant mean reduction from baseline in SBP compared with placebo at 8 weeks of therapy ($P \leq 0.05$), regardless of concurrent ACE inhibitor or ARB use. While eplerenone/ARB -treated patients exhibited a statistically significant mean reduction from baseline in DBP compared with placebo/angiotensin receptor blocker at 8 weeks of therapy ($P \leq 0.05$), patients receiving the eplerenone/ACE inhibitor combination therapy experienced a reduction in baseline DBP similar to placebo/ACE inhibitor therapy (*P* value not reported). Secondary: Significantly greater percentage of patients in the eplerenone/ARB groups exhibited a positive response to therapy compared to placebo/ARB -treated patients ($P=0.003$). No significant differences in response rate were observed between the eplerenone/ACE inhibitor and the placebo/ACE inhibitor groups (*P* value not reported). Adverse effects were mild-moderate and were similar in the eplerenone and placebo-treated groups (*P* value not reported).
Schersten et al[37] Spironolactone 50 mg daily vs spironolactone 100 mg daily	RCT, SB, XO Patients <75 years of age, with DBP between 105 to 135 mm Hg, after 10 to 15 minutes of supine rest	N=45 11 months	Primary: Change from baseline in DBP and SBP, adverse effects Secondary: Not reported	Primary: Each of the three spironolactone groups were associated with significantly reduced blood pressure levels from baseline as compared to placebo ($P<0.001$). While spironolactone 200 mg daily lowered mean supine SBP more than the spironolactone 50 mg daily therapy ($P<0.05$), the difference between spironolactone 50 mg and 100 mg/day was not statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs spironolactone 200 mg daily vs placebo once daily				significant (*P* value not reported). Spironolactone 200 mg daily was associated with a significant reduction in mean upright SBP from baseline compared with either of the lower dose groups (*P*<0.01). The difference in the lowering of DBP from baseline was not statistically different among any of the three active treatment groups (*P* value not reported). Spironolactone 100 mg/day therapy was associated with a statistically significant increase in baseline potassium and serum creatinine concentrations (*P*<0.05). However, spironolactone 50 mg was not associated with a change in potassium level from baseline (*P* value not reported). Secondary: Not reported
Weinberger et al[38] Eplerenone 50 mg once daily vs eplerenone 25 mg twice daily vs eplerenone 100 mg once daily vs eplerenone 50 mg twice daily	DB, MC, PG, RCT Patients 21 to 80 years of age, with seated, cuff-assessed DBP ≥95 mm Hg but <114 mm Hg, a 24-hour mean DBP >85 mm Hg; patients were excluded if they had secondary, severe, or malignant hypertension with or without retinopathy, used medications known to influence blood pressure, had a history of a myocardial infarction, percutaneous transluminal coronary	N=409 8 weeks	Primary: Mean change in seated DBP from baseline Secondary: Mean change from baseline in SBP, 24-hour SBP and DBP, renin, aldosterone levels	Primary: Eplerenone therapy, across all doses studied, was associated with a statistically significant reduction from baseline in seated and standing DBP compared to placebo (*P*<0.05). Eplerenone 50 mg twice daily regimen was associated with a statistically significant reduction in baseline seated and standing DBP compared to eplerenone 100 mg once daily group (*P*<0.05). However, there were no differences in DBP reduction between any of the other once daily and twice daily eplerenone regimens (*P* value not reported). Compared with placebo, spironolactone was associated with statistically significant reductions in DBP (*P*≤0.001). Eplerenone 50 mg twice daily and 100 mg daily regimens were associated with DBP reduction approximately comparable to 50%-75% of effect observed with spironolactone 50 mg twice daily therapy (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs eplerenone 400 mg once daily vs eplerenone 200 mg twice daily vs spironolactone 50 mg twice daily vs placebo	angioplasty, CABG, angina, intermittent claudication, severe aortic or mitral valvular disease, arrhythmia, cardiomyopathy, heart failure requiring digoxin or diuretic therapy, stroke, TIA, insulin-dependent diabetes, hepatic disease, serum creatinine >1.5 mg/dL or serum potassium >5 mEq/L, alcohol or drug abuse, night-shift employment, upper arm circumference >42 cm			Secondary: Eplerenone therapy, across all doses studied, was associated with a statistically significant reduction from baseline in seated and standing SBP compared to placebo ($P<0.05$). Eplerenone 200 mg twice daily regimen was associated with a statistically significant reduction in baseline seated and standing SBP compared to eplerenone 400 mg once daily group ($P<0.05$). However, there were no differences in SBP reduction between any of the other once daily and twice daily eplerenone regimens (*P* value not reported). Eplerenone, across all doses studied, was associated with a statistically significant reductions in ambulatory SBP and DBP compared with placebo, as observed during a 24-hour monitoring ($P<0.05$). Compared with placebo, spironolactone was associated with statistically significant reductions in SBP ($P\leq0.001$). Eplerenone 50 mg twice daily and 100 mg once daily regimens were associated with SBP reduction approximately comparable to 50% to 75% of effect observed with spironolactone 50 mg twice daily therapy (*P* value not reported). The incidence of adverse events in the eplerenone-treated patients was similar to placebo (*P* value not reported). Additionally, the incidence of adverse events was comparable in the eplerenone and spironolactone groups (*P* value not reported). Spironolactone 50 mg twice daily group was associated with a statistically significant increase from baseline in serum potassium level compared to the eplerenone 50 mg/day and 100 mg/day groups, regardless of once-daily or twice-daily dosing ($P<0.05$). Eplerenone therapy was not associated with an increased incidence of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				gynecomastia or impotence compared to placebo. There were no treatment-related menstrual abnormalities reported with eplerenone, while one patient in the spironolactone group reported treatment related intermenstrual bleeding.
White et al[39] Eplerenone 25 mg once daily vs eplerenone 50 mg once daily vs eplerenone 100 mg once daily vs eplerenone 200 mg twice daily vs placebo	DB, MC, RCT Adult patients, average age 53 years, with untreated hypertension and seated SBP <180 mm Hg, DBP between 95-110 mm Hg, and the 24-hour mean DBP ≥85 mm Hg; patients were excluded if they had a recent myocardial infarction, unstable angina, heart failure, clinically significant renal or liver disease, secondary hypertension, uncontrolled diabetes, serum potassium >5.00 mmol/L, or creatinine >1.5 (men) or >1.3 (women)	N=400 12 weeks	Primary: Mean change from baseline in seated DBP at 12 weeks Secondary: Change from baseline in SBP, 24-hour SBP and DBP, heart rate, adverse events	Primary: The eplerenone 50, 100, and 200 mg treatment groups experienced significant mean reductions in DBP from baseline compared to placebo ($P \leq 0.01$). The reduction in blood pressure in the eplerenone 25 mg group failed to meet statistical significance ($P=0.10$). Secondary: The eplerenone 50, 100, and 200 mg treatment groups experienced significant mean reductions in SBP from baseline compared to placebo ($P \leq 0.01$). All eplerenone treatment groups experienced statistically significant reductions in 24-hour ambulatory blood pressure measurements compared to placebo ($P<0.006$ for SBP and $P<0.005$ for DBP). There were no significant differences from baseline in 24-hour mean heart rate with any of the treatment groups compared to placebo (*P* value not reported). Treatment emergent adverse events were reported in 48% of the eplerenone-treated group and 49% of the placebo-treated group. None of the adverse events were statistically different between the groups (*P* value not reported). Two cases of impotence, gynecomastia, menstrual abnormalities and female breast pain were reported during the study; one case occurred in the placebo group and the other in the eplerenone 100 mg daily group.
White et al[40] Eplerenone 50 mg once daily, titrated up to 200 mg daily if needed for optimal blood pressure control (SBP <140 mm Hg)	AC, DB, MC, R Patients ≥50 years of age with systolic hypertension (seated clinic SBP 150 to 165 mm Hg with a pulse	N=269 24 weeks	Primary: Mean change from baseline in SBP, DBP, 24-hour ambulatory blood pressure, pulse pressure, and heart rate at week-24,	Primary: Mean reduction in SBP from baseline was comparable in the eplerenone and amlodipine groups ($P=0.83$). Eplerenone was associated with statistically significant reductions in DBP from baseline at 24 weeks of therapy compared to amlodipine ($P=0.014$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amlodipine 2.5 mg once daily, titrated up to 10 mg daily if needed for optimal blood pressure control	pressure ≥70 mm Hg or 165 to 200 mm Hg with a DBP ≤95 mm Hg); patients were excluded if had clinically significant heart, liver, or kidney disease, serum potassium ≥5.0 mmol/L, or serum creatinine >1.5 mmol/L or >1.3 mmol/L for men and women, respectively		albumin/creatinine ratio, adverse events Secondary: Not reported	The two treatment groups exhibited comparable decreases in 24-hour ambulatory blood pressure, pulse pressure, and heart rate after 24 weeks of therapy (*P*>0.05). Eplerenone was associated with a statistically significant reduction from baseline in the albumin/creatinine ratio compared to amlodipine (*P*=0.002). Treatment-emergent adverse events were reported in 64% of the eplerenone group and 70% of the amlodipine group. The only adverse event that was significant between the groups was the incidence of edema (25.5% for amlodipine vs. 3.7% for eplerenone; *P*<0.05). There were no reports of gynecomastia, breast tenderness, or menstrual irregularities in either group. Secondary: Not reported
Williams et al[41] Eplerenone 50 mg once daily, titrated up to 200 mg daily if needed for optimal blood pressure control (DBP <90 mm Hg) vs enalapril 10 mg once daily, titrated up to 40 mg daily if needed for optimal blood pressure control	AC, DB, MC, PG, R Men and nonpregnant women ≥18 years of age with stage 1 to 2 hypertension (seated DBP ≥90 but <110 mm Hg, with a seated SBP <190 mm Hg); patients were excluded if they had orthostatic hypotension, secondary, severe, or malignant hypertension, clinically significant laboratory abnormalities, hormone replacement therapy, history of diabetes, arrhythmia, heart	N=499 12 months	Primary: Change in seated trough DBP at month-6 Secondary: Change in seated trough SBP at month-6, reduction in SBP and DBP at month-12, reduction in UACR, adverse events	Primary: At 6 months of therapy both treatment groups exhibited comparable reductions in DBP from baseline (*P*=0.91). Secondary: At 6 months of therapy both treatment groups exhibited comparable reductions in SBP from baseline (*P*=0.20). At 12 months of therapy both treatment groups exhibited comparable reductions in SBP and DBP from baseline (*P*=0.25, *P*=0.33). Eplerenone was associated with a statistically significant reduction from baseline in UACR compared to enalapril (61.5% vs 25.7%; *P*=0.01). There were no significant differences in overall treatment-emergent adverse events between the two treatment groups (*P* value not reported). There were no sex hormone related adverse events in the eplerenone group. There were no clinically significant differences in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	failure, liver disease, myocardial infarction, coronary revascularization, unstable angina, stroke, or if DBP remained >90 mm Hg despite receiving the highest dose of study medication			the groups in any of the laboratory tests assessed. There were two patients in the eplerenone and two patients in the enalapril group that experienced hyperkalemia of ≥5.5 mmol/L.
Chapman et al.[42] ASCOT-BPLA Atenolol 50 to 100 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); bendroflumethiazide/K 1.25 to 2.5 mg and doxazosin were added for additional blood pressure control; if blood pressure remained elevated on three above drugs, spironolactone 25 mg was added to the regimen vs amlodipine 5 to 10 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); perindopril 4 to 8 mg and	SA Sub-analysis of the ASCOT-BPLA study, designed to evaluate effects of spironolactone on treatment-resistant hypertension. Men and women, aged 40 to 79 years with hypertension and ≥3 cardiovascular risk factors, with SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (not on antihypertensive therapy) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)	N=1,411 1.3 years	Primary: Change in DBP and SBP, adverse effects Secondary: Not reported	Primary: Spironolactone treatment lead to a significant 21.9 mm Hg reduction in SBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 20.8 to 23.0 mm Hg; *P*<0.001). Spironolactone treatment lead to a significant 9.5 mm Hg reduction in DBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 9.0 to 10.1 mm Hg; *P*<0.001). Spironolactone therapy was associated with small but significant decreases in sodium, low-density lipoprotein and total cholesterol as well as increases in potassium, glucose, creatinine, and high-density lipoprotein cholesterol (*P*<0.05). The most common adverse effect reported in the study was gynecomastia in men (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
doxazosin were added for additional blood pressure control; if blood pressure remained elevated on three above drugs, spironolactone 25 mg was added to the regimen				
Ogawa et al[43] Spironolactone 25 mg daily in addition to imidapril* 5 mg daily vs furosemide 20 mg daily in addition to imidapril* 5 mg daily All patients were pre-treated with imidapril* for one year prior to study onset.	PRO, R Patients, 62.3 years of age on average, with hypertension and type II diabetes, with a urinary albumin/creatinine ratio >30 mg/g creatinine, and plasma B-type natriuretic peptide levels >100 pg/mL (suggestive of mild heart failure)	N=30 24 months	Primary: Change in B-type natriuretic peptide, albumin/creatinine ratio, blood pressure Secondary: Not reported	Primary: At 12 months, spironolactone therapy was associated with a significant reduction in B-type natriuretic peptide level from baseline compared with spironolactone therapy ($P<0.05$). At 12 months, spironolactone therapy was associated with a significant reduction in albumin/creatinine ratio from baseline compared with spironolactone therapy ($P<0.05$). Both study groups exhibited similar reductions in blood pressure from baseline (*P* value not reported). No adverse events were reported in the study. Secondary: Not reported
Hood et al[44] SALT study Spironolactone 50 mg daily vs spironolactone 100 mg daily vs amiloride 20 mg daily	DB, RCT, XO Patients, 59.5 years of age on average, with seated blood pressure of 140/90 to 170/110 mm Hg, plasma renin of 12 mU/L, plasma aldosterone-renin ratio >750, previous fall in SBP ≥20 mm Hg after 1 month of open-label treatment with spironolactone 50 mg	N=57 42 weeks	Primary: Change in blood pressure and plasma renin from baseline between spironolactone 100 mg and bendroflumethiazide 5 mg daily regimens Secondary: Change in blood pressure and plasma renin from baseline between amiloride and	Primary: Spironolactone 100 mg and bendroflumethiazide 5 mg daily regimens were not associated with a statistically significant difference in blood pressure reduction from baseline (*P* value not reported). Secondary: Spironolactone 50 mg was associated with a statistically significant decrease in blood pressure from baseline compared with bendroflumethiazide 2.5 mg daily therapy ($P<0.01$). Losartan 100 mg was associated with a statistically significant decrease in blood pressure from baseline compared with bendroflumethiazide 2.5 mg daily therapy ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amiloride 40 mg daily vs bendroflumethiazide 2.5 mg daily vs bendroflumethiazide 5 mg daily vs losartan 100 mg daily vs placebo daily	daily; patients were excluded if they had secondary hypertension, contraindications to study drugs, or a history of hypokalemia		other diuretics and between lower and higher doses of each diuretic	High-dose bendroflumethiazide and amiloride regimens were associated with statistically greater reductions in blood pressure compared to the lower doses (*P*<0.05). Spironolactone was associated with a four-fold increase in baseline renin level compared to a two-fold increase observed with bendroflumethiazide therapy (*P*=0.003).
Taniguchi et al[45] Spironolactone 25 mg daily in addition to candesartan 8 mg daily for six months, after 6 months of candesartan monotherapy (combination group) vs candesartan 8 mg daily for 12 months	DB, RCT, XO Patients, 67 years of age on average, with essential hypertension and left ventricular hypertrophy	N=97 1 year	Primary: Change in blood pressure relative wall thickness Secondary: Not reported	Primary: Both study groups experienced a statistically significant reduction in blood pressure from baseline (*P*<0.05). While candesartan was associated with a significant reduction in relative wall thickness among patients with concentric left ventricular remodeling or hypertrophy (*P*<0.05), the addition of spironolactone did not provide additional benefit. Secondary: Not reported
Nephrotic Syndrome/Proteinuria				
Bianchi et al[46]	OL, PRO, R	N=165	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Spironolactone 25 mg daily in addition to conventional therapy (ACE inhibitor and/or ARB) vs conventional therapy (ACE inhibitor and/or ARB)	Patients, aged 54.7 years on average, with idiopathic chronic glomerulonephritis and proteinuria >1.0 g/g creatinine; patients were excluded if they had diabetes, renovascular or malignant hypertension, secondary glomerular disease, malignancies, myocardial infarction, stroke within 6 months, congestive heart failure, liver disease, serum potassium >5 mEq/L, or eGFR <30 mL/min/1.73 m^2	1 year	Change in proteinuria, eGFR, blood pressure, and serum potassium Secondary: Not reported	While there was a significant reduction in proteinuria from baseline among patients treated with spironolactone (*P*<0.001), there was no difference in the conventional therapy group (*P*>0.05). At one year, there was no significant difference between groups in eGFR (*P* value not reported). However, spironolactone treatment was associated with a lower monthly rate of decrease in eGFR from baseline compared conventional therapy (*P*<0.01). Patients whose baseline eGFR was <60 mL/min experienced a greater decline in eGFR compared to patients with baseline eGFR >60 mL/min (*P*<0.01). At one year of therapy, patients receiving spironolactone in addition to conventional therapy experienced a reduction in blood pressure from baseline (*P*<0.05). In contrast, those randomized to the conventional therapy group did not exhibit blood pressure reduction from baseline (*P* value not reported). While there was a significant increase in serum potassium from baseline among patients treated with spironolactone (*P*<0.001), there was no difference in the conventional therapy group (*P*>0.05). Secondary: Not reported
Chrysostomou et al[47] Spironolactone 25 mg daily, in addition to irbesartan 150 mg daily and ramipril 5 mg daily vs ramipril 5 mg daily, in addition to spironolactone 25 mg daily and irbesartan placebo	DB, PC, RCT Patients 18 to 75 years of age, with a 24-hour urinary protein excretion >1.5 g/24-hours on ≥2 occasions ≥3 months apart, serum creatinine level ≤200 µmol/L with <20% variability in the preceding 3 months, and treatment with an	N=41 6 months	Primary: Change in 24-hour urinary protein excretion at 3 months Secondary: Change in 24-hour urinary protein excretion at 6 months, change in blood pressure and creatinine clearance, adverse effects	Primary: Compared with the ramipril monotherapy group, the 24-hour urinary protein excretion reduction at 3-months was significantly greater in the ramipril and spironolactone groups (*P*=0.004). The ramipril, irbesartan, and spironolactone groups were associated with a significant reduction in 24-hour urinary protein excretion compared to the ramipril monotherapy group (*P*<0.001). There was no significant difference in 24-hour urinary protein excretion with the ramipril monotherapy group and the ramipril/irbesartan group (*P*=1.00).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ramipril 5 mg daily, in addition to spironolactone placebo and irbesartan 150 mg daily vs ramipril 5 mg daily, in addition to spironolactone and irbesartan placebos	ACE inhibitor ≥6 months			At three months of therapy, patients receiving spironolactone were associated with a significant reduction in proteinuria from baseline ($P \leq 0.001$). In contrast, those patients who were not receiving spironolactone did not experience a significant reduction in proteinuria from baseline ($P=0.840$). Secondary: At 6 months, patients receiving spironolactone therapy were associated with the greatest reduction in proteinuria compared to the other regimens ($P<0.05$). At 6 months, DBP was higher among patients randomized to the ramipril monotherapy group compared to other study regimens ($P=0.046$). There was no difference in SBP among the study groups (*P* value not reported). There were no differences in creatinine clearance among the study groups ($P>0.05$). Gynecomastia was not observed in any of the treatment groups.
Furumatsu et al[48] Spironolactone 25 mg daily added to ongoing therapy consisting of enalapril 5 mg daily and losartan 50 mg daily (triple blockade group) vs trichlor methiazide 1 mg or furosemide 10 mg daily added to ongoing therapy consisting of enalapril 5 mg daily and losartan 50 mg daily (control group)	MC, OL, PRO, RCT Patients 20 to 70 years of age, with controlled blood pressure <130/80 mm Hg, chronic nephropathy (defined by serum creatinine level <3 mg/dL or calculated creatinine concentration <30 mL/min), daily treatment with enalapril 5 mg and losartan 50 mg for at least 12 weeks, and persistent proteinuria (urinary	N=32 12 months	Primary: Reduction in proteinuria, urinary type IV collagen, SBP, DBP, mean blood pressure, creatinine, creatinine clearance, potassium, urinary aldosterone Secondary: Not reported	Primary: At one year of therapy, patients randomized to the triple blockage group experienced a statistically significant 58% reduction in urinary protein level from baseline ($P<0.05$); while there was no difference in the control group. Compared to the control group, the triple blockade group experienced a significant reduction in proteinuria at one year of therapy ($P<0.05$). At one year of therapy, patients randomized to the triple blockage group experienced a statistically significant 40% reduction in urinary type IV collagen from baseline ($P<0.05$); while there was no difference in the control group. However there was no statistically significant difference in the change of urinary type IV collagen from baseline between the two study groups (*P* value not reported). There were no statistically significant differences between the two study groups in the following outcome measures: SBP, DBP, mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	protein excretion >0.5 g/day)			blood pressure, creatinine, creatinine clearance, potassium, urinary aldosterone (*P* value not reported). Secondary: Not reported
van den Meiracker et al[49] Spironolactone 25 mg twice daily, in addition to ongoing antihypertensive therapy vs placebo twice daily, in addition to ongoing antihypertensive therapy	DB, PC, PG, RCT Patients, aged 34.5 years on average, with type 2 diabetes, macroalbuminuria (24-hour urinary albumin excretion >300 mg or urinary albumin to creatinine ratio >20 mg/mmol) despite use of an ACE inhibitor or ARB in recommended dosages for at least 1 year	N=59 1 year	Primary: Change in albuminuria, DBP and SBP, GFR, aldosterone level, plasma renin activity, and serum potassium Secondary: Not reported	Primary: Compared to placebo, spironolactone therapy was associated with a significant 40.6% reduction in albuminuria from baseline (*P*=0.002). Compared to placebo, spironolactone therapy was associated with a significant reduction in systolic blood pressure from baseline (*P*=0.04), with comparable reduction in DBP (*P* value not reported). Both groups exhibited comparable changes in GFR from baseline (*P* value not reported). Compared to placebo, spironolactone therapy was associated with significant increases in aldosterone level and plasma renin activity from baseline (*P*<0.05). There was a significant increase in serum potassium level with spironolactone therapy compared to placebo (*P*=0.02). Secondary: Not reported
Schjoedt et al[50] Spironolactone 25 mg daily, in addition to ongoing antihypertensive therapy (ACE inhibitor or ARB) vs placebo, in addition to ongoing antihypertensive	DB, RCT, XO Patients, aged 48.8 years on average, with diabetic nephropathy and nephrotic range albuminuria (>2,500 mg/24 hour) despite recommended antihypertensive treatment	N=20 2 weeks	Primary: Change in proteinuria, ambulatory DBP and SBP, GFR, fractional albumin clearance, aldosterone level, plasma renin activity, and serum potassium Secondary: Not reported	Primary: Compared to placebo, spironolactone therapy was associated with a significant 32% reduction in proteinuria from baseline (*P*<0.001). Compared to placebo, spironolactone therapy was associated with a significant reduction in systolic and diastolic ambulatory 24-hour blood pressures from baseline (*P*=0.004, *P*=0.001, respectively). Both groups exhibited comparable changes in GFR from baseline (*P*=0.13). Compared to placebo, spironolactone therapy was associated with a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapy (ACE inhibitor or ARB)				significant 31% reduction in fractional albumin clearance from baseline (*P*<0.001). Compared to placebo, spironolactone therapy was associated with significant increases in aldosterone level and plasma renin activity from baseline, 80% and 91%, respectively (*P*<0.005). While not significant, there was a trend towards an increase in the serum potassium level with spironolactone therapy compared to placebo (*P*=0.054). Secondary: Not reported

*Agent not available in the United States (US).
Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, I=international, MC=multi-center, OL=open label, PC=placebo-controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RR=relative risk, SA=sub-analysis, SB=single blind, XO=crossover study
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ARB=angiotensin II receptor blocker, β-blocker=β-adrenergic blocking agent, CABG=coronary artery bypass graft, DBP=diastolic blood pressure, EF=ejection fraction, eGFR=estimated glomerular filtration rate, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, LVEF=left ventricular ejection fraction, MRI=magnetic resonance imaging, NYHA=New York Heart Association, SBP=systolic blood pressure, SF-36=short form health survey, TIA=transient ischemic attack, UACR=urinary albumin: creatinine ratio

Additional Evidence

Dose Simplification:
All mineralocorticoid (aldosterone) receptor antagonists can be given in single or divided doses when used for the treatment of hypertension. In heart failure, spironolactone may be administered as a single or divided dose, whereas eplerenone is recommended for a once-daily administration.

A study by Ludbrook et al evaluated the differences in blood pressure control and adverse effect profile with 300 to 400 mg spironolactone administered either as a once-daily dose or in divided doses.[50] A total of 13 patients with moderate essential hypertension meeting the eligibility criteria participated in a randomized, double-blind, crossover, 42-day study. Both administration schedules were associated with comparable systolic and diastolic blood pressure reductions (*P* value not reported). In addition, the study suggests that neither the once daily nor the divided dose spironolactone regimen reduced the incidence of adverse effects. The incidence of adverse effects was high in both study groups (85%). The adherence rate in this study was 100%.

A study by Weinberger et al compared the following once daily and divided dose eplerenone regimens among 409 patients with hypertension: eplerenone 50 mg twice daily, eplerenone 100 mg once daily, eplerenone 25 mg twice daily, eplerenone 50 mg once daily, eplerenone 200 mg twice daily, and eplerenone 400 mg once daily.[37] Eplerenone 50 mg twice daily regimen was associated with a statistically significant reduction in baseline seated and standing diastolic blood pressure compared to eplerenone 100 mg once daily group ($P<0.05$). However, there were no differences in diastolic blood pressure reduction between any of the other once daily and twice daily eplerenone regimens (*P* value not reported).

A regimen of eplerenone 200 mg twice daily was associated with a statistically significant reduction in baseline seated and standing systolic blood pressure compared to eplerenone 400 mg once daily ($P<0.05$). However, there were no differences in systolic blood pressure reduction between any of the other once-daily and twice-daily eplerenone regimens (*P* value not reported).

An evidence-based medicine literature search did not reveal data on the effect of dosing schedules on adherence.

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact On Physician Visits:
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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

Relative Cost Index Scale	
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 10. Relative Cost of the Single Entity Mineralocorticoid (Aldosterone) Receptor Antagonists

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
eplerenone	tablet	Inspra®	$$$$	N/A
spironolactone	tablet	Aldactone®*	$$$$	$

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

X. Conclusions

The mineralocorticoid (aldosterone) receptor antagonists are indicated for the treatment of hypertension.[1-2] In addition, spironolactone is indicated for hyperaldosteronism, cirrhosis of the liver with edema/ascites, edematous conditions associated with congestive heart failure and/or nephrotic syndrome, as well as for the treatment of hypokalemia.[2] Eplerenone is indicated for the management of patients with congestive heart failure status post myocardial infarction, to increase survival.[1] Of note, while the RALES study demonstrated a survival benefit and a decrease in hospitalizations with spironolactone therapy, this agent is Food and Drug Administration (FDA) approved only for the management of edema secondary to congestive heart failure.[30]

In general, the incidence of side effects reported in clinical trials is similar with eplerenone and spironolactone therapies.[25-50] Either agent may cause an increase in serum potassium levels. However, compared to spironolactone, eplerenone is associated with a lower incidence of steroidal adverse effects, such as gynecomastia.[1-4] In the RALES study, gynecomastia or breast pain was reported in 10% of men treated with spironolactone, as compared to 1% of men receiving placebo (P=0.001).[30] The EPHESUS study reports sex hormone–related adverse events with eplerenone to be comparable to placebo.[26] In a study described by Weinberger et al. the overall incidence of adverse events was comparable in the eplerenone, spironolactone, and placebo groups (P value not reported).[37] However, the use of spironolactone at a dose of 50 mg twice daily was associated with a statistically significant increase from baseline in serum potassium levels, as compared to regimens of eplerenone 50 mg/day and 100 mg/day regardless of once-daily or twice-daily dosing (P<0.05). In addition, eplerenone therapy was not associated with an increased incidence of gynecomastia or impotence compared to placebo.

In addition to tolerability differences, aldosterone receptor antagonists differ in their pharmacokinetic parameters.[1-4] Eplerenone is extensively metabolized in the liver via the CYP3A4 system, leading to many interactions with other drugs. Consequently, eplerenone is contraindicated with concomitant use of potent CYP3A4 inhibitors. In contrast, spironolactone does not undergo metabolism via the CYP3A4 system and is therefore associated with a low risk for drug-drug interactions. Both agents may increase serum potassium and should not be administered with other drugs known to increase potassium level.

Aldosterone receptor antagonists have demonstrated efficacy in treating patients with moderate to severe symptoms of heart failure and reduced left ventricular ejection fraction in two landmark trials.[26,30] The RALES study found that patients with congestive heart failure New York Heart Association (NYHA) class IV randomized to spironolactone 25 mg daily therapy experienced a significant 30% reduction in mortality compared to placebo (P<0.001).[30] The EPHESUS study randomized patients with a history of myocardial infarction and congestive heart failure to eplerenone 25 to 50 mg daily or placebo.[26] In this study, eplerenone therapy was associated with a significant 15% reduction in all-cause mortality (P=0.001). A study by Karagiannis et al. found both aldosterone receptor antagonists to be comparable in reducing blood pressure among patients with bilateral idiopathic hyperaldosteronism.[32] Moreover, several studies evaluated the efficacy and safety of eplerenone and spironolactone in patients with primary hypertension.[33-44] Compared to placebo, both agents were associated with blood pressure reductions from baseline. There are no direct comparison trials between eplerenone and spironolactone for heart failure. Only one randomized controlled, multicenter study directly compared the two aldosterone receptor antagonists in patients with hypertension.[37] Both eplerenone and spironolactone regimens were associated with a statistically significant reduction from baseline in blood pressure compared to placebo

($P<0.05$). Eplerenone 50 mg twice daily and 100 mg daily regimens were associated with blood pressure reduction approximately comparable to 50% to 75% of effect observed with spironolactone 50 mg twice daily therapy (*P* value not reported).

In regards to treatment of hypertension, none of the clinical guidelines recommend one aldosterone receptor antagonist agent over another.[11-20] Many of the current clinical guidelines recommend the use of aldosterone antagonists as an add on therapy for hypertensive patients with certain compelling indications such as, post myocardial infarction or late stage heart failure. The guidelines recommend the use of aldosterone receptor antagonists in combination with an angiotensin converting enzyme inhibitor and a β blocker for patients who have had a myocardial infarction and have a left ventricular systolic dysfunction and signs of heart failure or those in NYHA functional class IV.[8-10] While spironolactone is FDA-approved for use in patients with edema secondary to nephrotic syndrome, the K/DOQI guidelines do not address the use of aldosterone receptor blockers for this indication.[19] The AACE guidelines acknowledge aldosterone antagonists to have a role in the treatment of small or bilateral adenomas, as an alternative to surgery. Eplerenone is recommended for male patients experiencing erectile dysfunction or gynecomastia with spironolactone therapy.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternative in general use.

XI. Recommendations

No brand single entity mineralocorticoid (aldosterone) receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Mineralocorticoid (Aldosterone) Receptor Antagonists
Combination Products
AHFS Class 243220
September 10, 2008

I. Overview

The class of combination mineralocorticoid (aldosterone) receptor antagonists includes one combination product, spironolactone and hydrochlorothiazide. This fixed-dose combination product is formulated for oral administration and is available generically. The individual agents have different, but complementary mechanisms and sites of action, leading to additive antihypertensive and diuretic effects.[1-3] Hydrochlorothiazide, a thiazide diuretic, increases the excretion of sodium and chloride by inhibiting their reabsorption from the ascending loop of Henle and early distal tubules of the kidney.[1,3] Spironolactone is an aldosterone receptor antagonist, also known as a mineralocorticoid receptor antagonist; it also functions as a potassium-sparing diuretic. It inhibits the aldosterone-mediated activity of the sodium-potassium exchange pump thereby leading to increased sodium/ water excretion and potassium reabsorption.[1,2] In effect, the spironolactone component of the combination product mitigates the potassium loss associated with the thiazide component. In addition, the decrease in sodium/water reabsorption and the inhibition of aldosterone contribute to diuresis as well as blood pressure reduction. Finally, spironolactone-hydrochlorothiazide has a role in conditions of excessive aldosterone secretion (i.e., edema, ascites).

The combination aldosterone receptor antagonist is Food and Drug Administration (FDA)-approved for the treatment of hypertension and edematous conditions secondary to cirrhosis of the liver, congestive heart failure, and nephrotic syndrome.[1] This spironolactone-hydrochlorothiazide combination product is contraindicated in patients with hyperkalemia, acute or significantly impaired renal function, allergy to thiazide diuretics, and may also be contraindicated in acute or severe hepatic failure. Caution is warranted when this agent is used concomitantly with potassium supplements or other medications that can increase potassium levels. Since spironolactone is not a selective mineralocorticoid receptor antagonist and may also antagonize glucocorticoid, progesterone, and androgen receptors, spironolactone-hydrochlorothiazide is associated with steroid-related adverse effects (eg, gynecomastia, impotence, menstrual abnormalities).[1,2,4] Gynecomastia is a dose-related adverse effect that is reversible upon discontinuation of therapy.[1] The FDA has issued a black box warning noting that fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Initially, patients should be treated with separate components of the combination product to determine their optimal dose. In addition, the FDA advises against unnecessary use of spironolactone, which has demonstrated tumorigenic activity in animal studies.

The combination mineralocorticoid (aldosterone) receptor antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Combination Mineralocorticoid (Aldosterone) Receptor Antagonists Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
spironolactone and hydrochlorothiazide	tablet	Aldactazide®*	spironolactone and hydrochlorothiazide

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the combination mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 2. For a comprehensive overview of the pharmacologic management of chronic heart failure and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Combination Mineralocorticoid (Aldosterone) Receptor Antagonists[5-18]

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[5]	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. • Aldosterone antagonists may be beneficial in patients with moderately severe-to-severe symptoms of heart failure with reduced left ventricular ejection fraction, though careful monitoring is required. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • Diuretics are recommended to control pulmonary congestion and peripheral edema. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[6]	Patients With Left Ventricular Systolic Dysfunction • An aldosterone antagonist may be added to the standard medication regimen (including diuretics) in patients who are in New York Heart Association (NYHA) functional class IV or those in class III previously in class IV (left ventricular ejection fraction ≤35%) from left ventricular systolic dysfunction. • An aldosterone antagonist should be considered in patients who have had an MI and who have symptomatic heart failure and left ventricular ejection fraction ≤40% while receiving standard therapy with an ACE inhibitor (or ARB) and a β-blocker. • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics are typically preferred. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • Diuretics are recommended in patients with evidence of fluid overload. Managing Patients With Heart Failure and Hypertension • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or CCB. • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing channel blocking agents (CCB) (amlodipine) may be considered. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary**	• ACE inhibitors are recommended in patients with left ventricular ejection fraction 40% to 45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention. • Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated.

Clinical Guideline	Recommendation
(2005)[7]	• Aldosterone antagonists are recommended in addition to ACE inhibitors, β-blockers, and diuretics in patients who have advanced heart failure (NYHA class III-IV) with systolic dysfunction, and in patients who are unable to tolerate therapy with ACE inhibitors. • Aldosterone antagonists are recommended in combination with an ACE inhibitor and a β-blocker in patients who have had a myocardial infarction (MI) and who have left ventricular systolic dysfunction and signs of heart failure. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[8]	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia. • Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and

Clinical Guideline	Recommendation
	should not be used in patients whose potassium levels are greater than 5.0 mEq/L. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)[9]**	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors). • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)[10]**	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)[11]**	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients. • Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
National Institute for Health and Clinical Excellence (NICE)/British	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth

Clinical Guideline	Recommendation
Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[12]	medication or consult a specialist. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[13]	• No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[14]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2. • Multiple drug therapy is generally required to achieve blood pressure goals. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[15]	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[16]	• ACE inhibitors and ARBs have many advantages for patients with chronic kidney disease (CKD) and associated comorbid medical conditions. They slow the progression of diabetic kidney disease and nondiabetic kidney disease with proteinuria, and in addition, they reduce proteinuria, irrespective of the type of kidney disease. • ACE inhibitors are more effective than other antihypertensive agents in slowing the progression of most nondiabetic kidney diseases. The beneficial effect is greater in patients with severe proteinuria. • ARBs may be more effective than other antihypertensive agents in slowing the progression of nondiabetic kidney disease. • ACE inhibitors and ARBs in combination may be more effective than either alone in slowing the progression of nondiabetic kidney disease. • Diuretics may potentiate the beneficial effects of ACE inhibitors and ARBs in nondiabetic kidney disease. • ACE inhibitors, ARBs, and nondihydropyridine calcium-channel blockers have a greater antiproteinuric effect than other antihypertensive classes in nondiabetic kidney disease. • Dihydropyridine calcium-channel blockers are less effective than other agents in slowing the progression of nondiabetic kidney disease with proteinuria. • The K/DOQI guidelines do not address the use of aldosterone receptor antagonists for the management of nondiabetic kidney disease.
American Association for the Study of Liver Diseases (AASLD): **Management of Adult Patients with Ascites due to Cirrhosis (2004)**[17]	• A goal of treatment is to increase urinary sodium excretion to >78 mmol per day. • The guidelines recommend dietary sodium restriction (2,000 mg per day) and diuretic therapy as first line treatment in patients with ascites and cirrhosis. • Only patients who achieve urinary sodium excretion of > 78 mmol per day can bypass diuretic therapy. • The typical diuretic regimen consists of single morning doses of spironolactone, beginning with 100 mg, in addition to furosemide 40 mg. Single morning dosing improves adherence. • Spironolactone monotherapy may be used only in patients who have minimal fluid

Clinical Guideline	Recommendation
	overload. • The doses of spironolactone and furosemide may be increased every 3 to 5 days for adequate natriuresis; however, the 100/40 mg ratio should be maintained to avoid hyperkalemia. • The maximum spironolactone and furosemide daily doses are 400 and 160 mg, respectively. • In patients experiencing painful gynecomastia with spironolactone, amiloride (10 to 40 mg daily) may be an appropriate substitute. However, amiloride is more expensive and has been shown to be less effective than an active metabolite of spironolactone (potassium canrenoate) in a controlled, clinical trial. • Fluid restriction is not necessary unless serum sodium is less than 120 to 125 mmol/L. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses. • Liver transplantation should be considered in patients with cirrhosis and ascites. • Refractory ascites is defined as ascites unresponsive to sodium-restricted diet and high-dose diuretics (spironolactone 400 mg/day and furosemide 160 mg/day) • Serial therapeutic paracenteses may be performed in refractory ascites patients. • Referral for liver transplantation should be expedited in patients with refractory ascites. • Transjugular intrahepatic portasystemic stent shunt (TIPS) should be considered in appropriate patients. • Peritoneovenous shunt should be considered for patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS.
World Gastroenterology Organization (WGO) Practice Guideline. **Management of Ascites Complicating Cirrhosis in Adults**[18]	• A goal of treatment is to increase urinary sodium excretion to >78 mmol per day. • Initial oral diuretic therapy consists of single daily doses of spironolactone 100 mg, or spironolactone 100 mg in addition to furosemide 40 mg. • If used as monotherapy, spironolactone dose may be increased up to 400 mg daily. If used in combination with furosemide, the dose of both agents may be increased while maintaining the 2/5 ratio. • The maximum daily doses of spironolactone and furosemide are 400 and 160 mg, respectively. • Spironolactone monotherapy is more effective compared to furosemide monotherapy. However its use should be restricted to patients exhibiting minimal fluid overload. • Spironolactone monotherapy may be complicated by hyperkalemia and gynecomastia. Amiloride and triamterene are substitutes for spironolactone. • Indications of diuretic resistance include minimal to no weight loss and urinary sodium excretion of <78 mmol/day. Diuretic therapy should be discontinued in patients who develop encephalopathy, clinically significant complications of diuretics, hyperkalemia, metabolic acidosis with spironolactone, and whose serum sodium is <120 mmol/L or serum creatinine >2 mg/dL. • Serial large-volume paracenteses are safe and effective in patients with refractory ascites. Other potential treatment options for diuretic-refractory ascites are TIPS, peritoneovenous shunt, and liver transplantation.

III. Indications

Food and Drug Administration (FDA)-approved indications for the combination mineralocorticoid (aldosterone) receptor antagonists 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 Combination Mineralocorticoid (Aldosterone) Receptor Antagonists[1]

Indication	Spironolactone and Hydrochlorothiazide*
Essential hypertension	✔ †
Edematous conditions for patients with:	
Congestive heart failure	✔ ‡
Liver cirrhosis with edema and/or ascites	✔ § (maintenance therapy)
Nephrotic syndrome	✔ ‖

*The fixed-dose combination product is not indicated for initial treatment of hypertension or edema. These conditions require the single components to be titrated to effect. If the single agents are being used at equivalent doses of the fixed-dose combination product, the combination may be more convenient for patient management.
†For patients in whom other measures are inadequate or inappropriate.
‡For the management of edema and sodium retention when the patient is only partially responsive to, or is intolerant of other therapies; also indicated for patients receiving digitalis, or in patients with diuretic-induced hypokalemia when other therapies are inappropriate.
§Aldosterone levels may be high in this condition. In addition to pharmacotherapy and bed rest, fluid and sodium intake should be restricted.
‖May be used when treatment of the underlying condition, fluid and sodium intake restriction, as well as the use of other diuretics do not provide an adequate response.

IV. Pharmacokinetics

The pharmacokinetic parameters for the combination mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Combination Mineralocorticoid (Aldosterone) Receptor Antagonists[1,4,19-21]

Drug(s)	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Spironolactone	~73*	>90	Hepatic, renal	Yes, canrenone, 7-α-thiomethylspironolactone, 6-β-hydroxy-7-α-thiomethylspironolactone	Urine: 47-57 Feces: 35-41	1.3-1.4
Hydrochlorothiazide	50-75	40-68	Not appreciably metabolized	Not reported	Urine	6-15

* Food increases the spironolactone absorption by almost 100%. However the clinical implication of this effect is unknown.

V. Drug Interactions

Significant drug interactions with the combination mineralocorticoid (aldosterone) receptor antagonists are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Combination Mineralocorticoid (Aldosterone) Receptor Antagonists[22]

Drug(s)	Significance Level	Interaction	Mechanism
Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	1	Potassium supplements (potassium acetate, potassium acid phosphate, potassium bicarbonate, potassium chloride, potassium citrate, potassium gluconate, potassium iodide, potassium phosphate)	Coadministration of potassium supplements with potassium-sparing diuretics may result in increased potassium serum concentrations and consequently an increased risk of severe hyperkalemia. This combination should not be used without documented evidence of hypokalemia unresponsive to either agent alone. If the combination is required, closely monitor serum potassium concentrations.

Drug(s)	Significance Level	Interaction	Mechanism
Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	1	Angiotensin-converting enzyme (ACE) inhibitors (all)	ACE inhibitors in combination with potassium-sparing diuretics may increase serum potassium concentrations in certain high-risk (i.e., renally impaired) patients via an unknown mechanism. Adjust dose as necessary; monitor patients' renal function and serum potassium levels.
Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	1	Angiotensin II receptor antagonists (ARBs) (all)	ARBs in combination with potassium-sparing diuretics may increase serum potassium concentrations in certain high-risk (i.e., renal impairment, type 2 diabetes) patients, via an unknown mechanism, leading to additive or synergistic effects. Adjust dose as necessary; monitor patients' renal function and serum potassium levels.
Hydrochlorothiazide	1	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Hydrochlorothiazide	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Spironolactone	2	Digoxin	Spironolactone may decrease the positive inotropic effect of digoxin via its own negative inotropic effect. Spironolactone interferes with the tubular secretion of digoxin, leading to decreased clearance and increased digoxin plasma concentration. Adjust digoxin dose as necessary; monitor patients closely.
Hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Hydrochlorothiazide	2	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Hydrochlorothiazide	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate carefully in small or intermittent doses.

Drug(s)	Significance Level	Interaction	Mechanism
Hydrochlorothiazide	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

Combination mineralocorticoid (aldosterone) receptor antagonists may cause a transient elevation of blood urea nitrogen, increase/decrease of potassium level, and other electrolyte disturbances.[1] Patients should be observed for signs and symptoms of fluid or electrolyte abnormality. If hyperkalemia develops, the medication should be discontinued. In addition, spironolactone has been associated with steroidal adverse events, such as gynecomastia in men, sexual dysfunction, and menstrual irregularity. In addition, this product should be discontinued before performing parathyroid function evaluation due to the potential of thiazide diuretics to induce hypercalcemia. The fixed-dose combination product is not indicated for initial therapy of edema or hypertension. The appropriate dose of the fixed-dose combination product should be established by the titration of its individual components. The most common adverse reactions reported with the combination mineralocorticoid (aldosterone) receptor antagonists are noted in Table 6.

In addition spironolactone has been shown to be a tumorigenic in chronic toxicity studies in rats. This has resulted in the black box warning outlined in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Combination Mineralocorticoid (Aldosterone) Receptor Antagonists [1,4,19-21]

Adverse Event	Hydrochlorothiazide	Spironolactone
Cardiovascular		
Edema	-	✔
Orthostatic hypotension	✔	-
Central Nervous System		
Ataxia	-	✔
Blurred vision	✔	-
Dizziness/lightheadedness	✔	-
Drowsiness	-	✔
Fatigue	-	✔
Fever	✔	✔
Headache	✔	✔
Lethargy	-	✔
Mental confusion	-	✔
Restlessness/insomnia	✔	-
Vertigo	✔	-
Weakness	✔	-
Xanthopsia	✔	-
Dermatological		
Alopecia	✔	-
Anaphylactic reactions	✔	✔
Exfoliative dermatitis/toxic epidermal necrolysis	✔	-
Erythema multiforme, Stevens-Johnson syndrome	✔	-
Maculopapular/erythematous cutaneous eruptions	-	✔
Necrotizing angiitis	✔	-

Adverse Event	Hydrochlorothiazide	Spironolactone
Photosensitivity/photosensitivity dermatitis	✔	-
Pruritus	✔	-
Purpura	✔	-
Rash	✔	-
Urticaria	✔	✔
Vasculitis, cutaneous vasculitis	✔	✔
Endocrine and Metabolic		
Amenorrhea	-	✔
Breast carcinoma	-	✔
Deepening of the voice	-	✔
Glycosuria	✔	-
Gynecomastia	-	≤ 52.2
Hirsutism	-	✔
Hyperchloremic metabolic acidosis	-	✔
Hyperglycemia	✔	-
Hyperkalemia	-	≤ 40
Hyperuricemia	✔	-
Hyponatremia	-	✔
Irregular menses	-	✔
Mastodynia	-	2
Postmenopausal bleeding	-	✔
Gastrointestinal		
Abdominal pain/cramping/bloating	✔	✔
Anorexia	✔	-
Cholestatic/hepatocellular toxicity	-	✔
Constipation	✔	-
Diarrhea	✔	✔
Gastric bleeding	-	✔
Gastric irritation/gastritis/epigastric distress	✔	✔
Jaundice	✔	-
Nausea	✔	✔
Pancreatitis	✔	-
Sialoadenitis	✔	-
Ulceration	-	✔
Vomiting	✔	✔
Genitourinary		
Impotence/reduced libido/erectile dysfunction	✔	✔
Interstitial nephritis	✔	-
Renal failure/dysfunction	✔	✔
Hematologic		
Agranulocytosis	✔	✔
Aplastic/hypoplastic anemia	✔	-
Eosinophilia	-	✔
Hemolytic anemia	✔	-
Leukopenia	✔	-
Thrombocytopenia	✔	✔
Laboratory Test Abnormalities		
Blood urea nitrogen increased	-	✔
Decreased sodium	-	✔
Increased potassium	-	✔
Other		
Breast cancer	-	✔

Adverse Event	Hydrochlorothiazide	Spironolactone
Muscle cramps/spasm	✔	-
Respiratory distress (pneumonitis/pulmonary edema)	✔	-

✔ Percent not specified or incidence <1%.
-Event not reported.

Table 7. Black Box Warning for Spironolactone-Hydrochlorothiazide[1]

Warning
Spironolactone, an ingredient of spironolactone-hydrochlorothiazide, has been shown to be a tumorigenic in chronic toxicity studies in rats. Spironolactone-hydrochlorothiazide should be used only in those conditions for which it is indicated. Unnecessary use of this drug should be avoided. Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static but must be reevaluated as conditions in each patient warrant.

VII. Dosing and Administration

Combination mineralocorticoid (aldosterone) receptor antagonists are associated with a risk of hyperkalemia.[1] This risk is increased with declining renal function and higher dosages.[2] In addition, elderly patients have been noted to have an increased risk of hyperkalemia with spironolactone therapy; consequently, lower initial doses should be considered. Consequently, routine monitoring of potassium levels and renal function is recommended. Optimal doses should be established by individual titration of the separate components.[1] The usual dosing regimens for the combination mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 8.

Table 8. Usual Dosing for the Combination Mineralocorticoid (Aldosterone) Receptor Antagonists[1,4]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Spironolactone and hydrochlorothiazide*	Edema (congestive heart failure, hepatic cirrhosis, or nephrotic syndrome)†, ‡: Maintenance, 100/100 mg daily in single or divided doses, may range from 25/25 to 200/200 mg daily Essential hypertension: Maintenance, 50/50 to 100/100 mg daily in single or divided doses	Safety and efficacy in children have not been established.	Tablet: 25/25 mg 50/50 mg

* Concurrent potassium supplementation is not recommended
†Separate tablets of either spironolactone or hydrochlorothiazide may be administered in adjunction with Aldactazide to provide optimal individual therapy.
‡The onset of diuresis may occur rapidly and persist for 2 to 3 days after therapy discontinuation.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the combination mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Combination Mineralocorticoid (Aldosterone) Receptor Antagonists[21-23]

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Levy[23] Spironolactone 25 mg daily, HCTZ 25 mg daily, combination entity, for 16 weeks following 8 weeks of furosemide monotherapy vs furosemide 25 mg daily for 24 weeks	DB, RCT Patients, aged 27 to 79 years, with arteriosclerotic heart disease, hypertensive heart disease, or rheumatic heart disease classes I-III, and congestive heart failure requiring diuretic therapy; patients were excluded if had a history of acute pulmonary edema, hydrothorax, ascites, or anasarca during the previous 12 months, malignancy, severe liver disease, serum creatinine ≥2 mg/100 mL	N=32 24 weeks	Primary: Change in heart failure symptoms, glucose, renin concentration, calcium, blood urea nitrogen, uric acid, creatinine, aldosterone, serum potassium level, adverse effects Secondary: Not reported	Primary: The combination therapy group and furosemide monotherapy group exhibited comparable control of heart failure symptoms (*P* value not reported). The combination therapy group was associated with a significant decrease in glucose and an increase in plasma renin concentration compared to furosemide monotherapy group ($P<0.01$). There were no significant differences in calcium, blood urea nitrogen, uric acid, or creatinine between the study groups (*P* value not reported). There was a significant increase in aldosterone secretion among patients randomized to the spironolactone and HCTZ group compared to the furosemide group ($P<0.01$). There was no significant difference in serum potassium level between treatment groups (*P* value not reported). No serious adverse effects were observed in either of the study groups. Secondary: Not reported
Nash[24] Spironolactone 50 mg twice daily vs spironolactone 100 mg	DB, RCT Male outpatients between the ages of 21 to 65 years, with essential hypertension, DBP between 90 to 114 mm Hg; patients were	N=79 12 weeks	Primary: Change in SBP, DBP, blood urea nitrogen, serum potassium, gynecomastia Secondary: Not reported	Primary: At week-12, all study groups exhibited significant reductions in SBP and DBP from baseline ($P<0.05$). At week-12, all 3 spironolactone monotherapy groups exhibited statistically significant increases in blood urea nitrogen from baseline ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
twice daily vs spironolactone 200 mg twice daily vs HCTZ 50 mg twice daily vs spironolactone 25 mg and HCTZ 25 mg one capsule twice daily, combination entity	excluded if they had DBP >114 mm Hg, severe renal, hepatic, endocrine, gastrointestinal disease, recent myocardial infarction, congestive heart failure, or severe angina			At week-12, the HCTZ monotherapy group was associated with a statistically significant decrease in serum potassium levels (*P*<0.001). At week-12, all 3 spironolactone monotherapy groups exhibited statistically significant increases in serum potassium levels from baseline (*P*<0.05). At week-12, the spironolactone-hydrochlorothiazide combination group was not associated with statistically significant increases in serum potassium levels from baseline (*P* value not reported). A dose-related risk of gynecomastia was observed in the spironolactone-treated patients. Among patients treated with spironolactone 50, 100, or 200 mg twice daily, 5.5%, 11.8%, and 40% reported gynecomastia symptoms. Of the patients randomized to spironolactone/hydrochlorothiazide combination product, 7.7% reported gynecomastia symptoms. Secondary: Not reported
Schrijver et al[25] Spironolactone 50 mg twice daily for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IA) vs spironolactone 50 mg twice daily for 8 weeks (single drug phase), subsequently HCTZ 50 mg twice daily was added to the regimen for an additional 4 weeks	C, DB Patients, between 24 to 63 years of age, with DBP between 90 to 114 mm Hg; patients were excluded if they had secondary hypertension, congestive heart failure, angina, blood urea nitrogen >25 mg%	N=49 20 weeks (4-week placebo run-in, 8-week single drug therapy, 4-week two-drug therapy, 4-week recovery)	Primary: Change in MABP, serum potassium, uric acid level, blood glucose, blood urea nitrogen, creatinine, plasma renin activity, aldosterone, side effects Secondary: Not reported	Primary: Following 8 weeks of therapy with a single drug, all study groups exhibited a statistically significant reduction in MABP from baseline (*P*<0.01). There were no significant differences in MABP reduction among the study groups (*P* value not reported). The addition of a second drug to the antihypertensive regimen was not associated with a significant improvement in MABP (*P* value not reported). At the end of the two-drug treatment period, there were no differences in MABP among any of the study groups (*P* value not reported). Spironolactone therapy was associated with a significant decrease in serum potassium concentration from baseline (*P*<0.001). Spironolactone regimens were not associated with a significant change in potassium levels from baseline (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(group IB) vs spironolactone 100 mg twice daily for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IIA) vs spironolactone 100 mg twice daily for 8 weeks (single drug phase), subsequently HCTZ 50 mg twice daily was added to the regimen for an additional 4 weeks (group IIB) vs spironolactone 200 mg twice daily for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IIIA) vs spironolactone 200 mg twice daily for 8 weeks (single drug phase), subsequently HCTZ 50 mg				Following 8 weeks of therapy with a single drug, HCTZ-treated patients experienced a statistically significant increase in uric acid from baseline (*P*<0.001). Groups IIA and IIB also experienced a significant but smaller increase in uric acid level from baseline (P<0.05) with no change in groups I and IV. During the single-drug treatment phase, patients randomized to group I experienced a significant increase in blood glucose from baseline (*P*<0.05). During the single-drug treatment phase, all patients except those randomized to group I experienced a significant increase in blood urea nitrogen from baseline (*P*<0.05). During the single-drug treatment phase, patients randomized to groups I and II experienced a significant increase in serum creatinine from baseline (*P*<0.05). During the single-drug treatment phase, all treatment groups experienced a significant increase in plasma renin activity from baseline (*P*<0.01). The addition of HCTZ in the two-drug study phase was associated with a rise in plasma renin activity in all study groups (*P*<0.05). All treatment groups experienced a significant increase in plasma aldosterone from baseline (*P*<0.05). Gynecomastia was reported only by patients randomized to the higher-dose spironolactone groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
twice daily was added to the regimen for an additional 4 weeks (group IIIB) vs hydrochlorothiazide 50 mg twice daily for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IVA) vs hydrochlorothiazide 50 mg twice daily for 8 weeks (single drug phase), subsequently HCTZ 50 mg twice daily was added to the regimen for an additional 4 weeks (group IVB)				

Study abbreviations: C=controlled, DB=double blind, RCT=randomized controlled trial
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, MABP=mean arterial blood pressure, SBP=systolic blood pressure

Additional Evidence

Dose Simplification:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Combination Mineralocorticoid (Aldosterone) Receptor Antagonists

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
spironolactone and hydrochlorothiazide	tablet	Aldactazide®*	$$$$	$

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

X. Conclusions

The combination mineralocorticoid (aldosterone) receptor antagonists are indicated for the treatment of essential hypertension and edematous conditions secondary to congestive heart failure, cirrhosis, and nephrotic syndrome.[1] However, the fixed-dose spironolactone-hydrochlorothiazide product is not indicated for initial therapy of these conditions. Patients may be switched to the combination drug after stabilization on its individual components. In general, the side-effect, pharmacokinetic, and drug-drug interaction profiles of the fixed-dose, spironolactone-hydrochlorothiazide combination product are comparable to those of its separate constituents.[1-4,22] It is contraindicated in patients with hyperkalemia, acute or significantly impaired renal function, and allergy to thiazide diuretics, and may also be contraindicated in acute or severe hepatic failure, and should be used with caution in patients taking agents known to increase potassium levels.[1] In addition, spironolactone-hydrochlorothiazide is associated with steroid-related adverse effects (eg, gynecomastia, impotence, menstrual abnormalities).[1,2,4] Finally, this product should only be used when indicated and should be avoided in patients with appropriate therapy alternatives since spironolactone has demonstrated tumorigenic activity in animal studies.[1]

Many patients with hypertension will require two or more medications to reach their blood pressure goals.[8-16] International practice guidelines recommend initiating treatment of Stage II or III hypertension with medications from two different antihypertensive classes.[8,9,11] A thiazide diuretic is the preferred antihypertensive agent to be used as part of a combination regimen. Moreover, many patients with congestive heart failure require diuretic therapy for symptomatic relief.[5-7] Aldosterone receptor antagonists are recommended as adjunct therapy to the standard congestive heart failure regimen (including diuretics) for patients in NYHA functional class IV or congestive heart failure secondary to a myocardial infarction. While a fixed-dose combination aldosterone antagonist product may offer improved compliance and convenience, it is not associated with a clinical advantage over its individual components when coadministered.[23-24] In addition, the fixed-dose combination product is not indicated for initial use and should be initiated only after a gradual titration of its individual components, coadministered.[1]

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternative in general use.

XI. Recommendations

No brand combination mineralocorticoid (aldosterone) receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Renin Inhibitors
Single Entity Agents
AHFS Class 243240
September 10, 2008

I. Overview

Aliskiren (Tekturna®) is the only direct renin inhibitor available in the United States (US). It was approved by the Food and Drug Administration (FDA) on March 5, 2007 for the treatment of hypertension, either as monotherapy or in combination with other antihypertensive agents.[1,2]

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[3] Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is the first and rate-limiting step of the RAAS.[2-5] Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II can increase blood pressure by direct vasoconstriction and stimulation of catecholamine release. In addition, angiotensin II induces aldosterone secretion, leading to sodium and fluid retention.[5] Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy, inflammation, remodeling, and thrombosis. Through a negative feedback mechanism, angiotensin II inhibits renin release.[2] As a direct renin inhibitor, aliskiren reduces angiotensin I, angiotensin II and aldosterone levels by binding to renin with high affinity in the plasma.[4,5] All drugs that inhibit RAAS, including aliskiren, can suppress the negative feedback loop and cause a compensatory increase in plasma renin concentrations. Aliskiren blocks the effects of increased renin levels.[2] The effects of aliskiren on other components of the RAAS are not known.

The single entity renin inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Single Entity Renin Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
aliskiren	tablet	Tekturna®	none

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

As noted above, Tekturna® was the first single entity renin inhibitor marketed in the United States, and it was approved by the Food and Drug Administration (FDA) in March 2007 for the management of hypertension.[1] Table 2 outlines the current national and international treatment guidelines for the pharmacologic management of hypertension. At this time, none of these guidelines have incorporated recommendations regarding the use of renin inhibitors, either the single entity agents or fixed-dose combination products. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines for the Single Entity Renin Inhibitors

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)[6]**	• The use of renin inhibitors was not addressed in this guideline.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)[7]**	• The use of renin inhibitors was not addressed in this guideline.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)[8]**	• The use of renin inhibitors was not addressed in this guideline.
Treatment Guidelines From the Medical Letter on Drugs and Therapeutics:	• The use of renin inhibitors was not

Clinical Guideline	Recommendation(s)
Drugs for Hypertension (2005)[9]	addressed in this guideline.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[10]	• The use of renin inhibitors was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes–2008**[11]	• The use of renin inhibitors was not addressed in this guideline.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[12]	• The use of renin inhibitors was not addressed in this guideline.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[13]	• The use of renin inhibitors was not addressed in this guideline.

III. Indications

FDA-approved indications for the single entity renin inhibitors are noted in Table 3. While this agent 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 Single Entity Renin Inhibitors[2]

Drug	Indication
Aliskiren	Treatment of hypertension, either alone or in combination with other antihypertensive agents; use with maximal doses of angiotensin-converting enzyme inhibitors has not been adequately studied

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity renin inhibitors are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Single Entity Renin Inhibitors[2,14]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination	Half-Life (hours)
Aliskiren	2.5	49.5	Liver, extent unknown*	Unknown	25% unchanged in the urine	24

*In vitro studies indicate that the major enzyme responsible for aliskiren metabolism appears to be CYP3A4.

V. Drug Interactions

Significant drug interactions reported with the single entity renin inhibitors are summarized in Table 5. Since aliskiren has been associated with infrequent increases in serum potassium of >5.5 meq/L (0.9% vs 0.6% with placebo), caution should be exercised with concomitant use of aliskiren with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that increase potassium levels.[2,14]

Table 5. Significant Drug-Drug Interactions with the Single Entity Renin Inhibitors[2,14]

Drug	Significance Level	Interaction	Mechanism
Aliskiren	2	Angiotensin-converting enzyme (ACE) inhibitors	Aliskiren has been associated with infrequent increases in serum potassium of >5.5 meq/L (0.9% vs 0.6% with placebo). When aliskiren was used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Use caution when aliskiren is given concomitantly with ACE inhibitors. Routine monitoring of electrolytes and renal function is indicated in this population.

Drug	Significance Level	Interaction	Mechanism
Aliskiren	2	Atorvastatin	Concurrent administration of aliskiren with atorvastatin (a CYP3A4 substrate) led to a 50% increase in aliskiren area under the curve (AUC) and maximum concentration (C_{max}) following multiple dosing. Caution is advised if aliskiren is administered concurrently with atorvastatin.
Aliskiren	2	Furosemide	Concurrent administration of aliskiren with furosemide resulted in decreases of 30% and 50% in furosemide AUC and C_{max}, respectively. Caution is advised if these agents are coadministered.
Aliskiren	2	Ketoconazole	Concurrent administration with ketoconazole (CYP3A4 inhibitor) at 200 mg twice daily led to an 80% increase in plasma levels of aliskiren. Caution is advised if administered concurrently with ketoconazole.
Aliskiren	Unknown*	Cyclosporine	Coadministration of 200 mg and 600 mg cyclosporine with 75 mg aliskiren resulted in 2.5 and 5 fold increases in C_{max} and AUC, respectively. Concomitant use of aliskiren with cyclosporine is not recommended.
Aliskiren	Unknown*	Irbesartan	Irbesartan reduced the maximum concentration of aliskiren by up to 50% after multiple dosing. The clinical significance of this interaction was not reported.

*The significance level of this interaction was not reported.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the single entity renin inhibitors are summarized in Table 6.

Table 6. Adverse Drug Events (%) Reported for the Single Entity Renin Inhibitors[2]

Adverse Event	Aliskiren
Cardiovascular	
Hypotension	<1 (severe)
Central Nervous System	
Dizziness	✔
Fatigue	✔
Headache	✔
Seizure	<1
Dermatologic	
Rash	1
Gastrointestinal	
Abdominal pain	<1
Diarrhea	1-2
Dyspepsia	<1
Gastroesophageal reflux	<1
Hematologic	
Anemia	<1
Hematocrit decreased	<1
Hemoglobin decreased	<1
Hypersensitivity	
Angioedema	<1
Metabolic	
Gout	<1
Hyperkalemia	1*
Uric acid increased	<1
Musculoskeletal	
Creatine kinase increased (>300%)	1
Myositis	<1

Adverse Event	Aliskiren
Rhabdomyolysis	<1
Renal	
Blood urea nitrogen increased	≤7
Renal stone formation	<1
Serum creatinine increased	≤7
Respiratory	
Cough	1†
Nasopharyngitis	✔
Upper respiratory infection	✔
Other	
Back pain	✔
Edema (face, hands, or whole body)	<1
Periorbital edema	✔

✔ Percent not specified.
*The incidence of hyperkalemia was 1% with monotherapy and 6% with concurrent angiotensin-converting enzyme (ACE) inhibitor therapy in patients with diabetes.
†In active-controlled trials with ramipril and lisinopril, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Table 7. Black Box Warning for the Single Entity Renin Inhibitors[2]

WARNING: AVOID USE IN PREGNANCY
When used in pregnancy drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, aliskiren should be discontinues as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

VII. Dosing and Administration

The usual dosing regimens for single entity renin inhibitors are summarized in Table 8.

Table 8. Usual Dosing for the Single Entity Renin Inhibitors[2]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Aliskiren	Hypertension: Initial, 150 mg once daily; may increase daily dose to 300 mg if blood pressure not adequately controlled; antihypertensive effect of a given dose is substantially attained (85%-90%) by 2 weeks; doses above 300 mg did not give an increased blood pressure response but increased the rate of diarrhea	Safety and efficacy in children have not been established.	Tablet: 150 mg 300 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity renin inhibitors are found in Table 9.

Table 9. Comparative Clinical Trials Using Single Entity Renin Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oh et al[15] Aliskiren 150 mg, 300 mg or 600 mg QD vs placebo	DB, MC, PC, PG, RCT Men and women ≥18 years (mean age 53 years) with mild-to-moderate essential hypertension (DBP ≥95 and <110 mm Hg)	N=672 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, 24-hour ABPM, proportion achieving a successful treatment response (defined as DBP <90 mm Hg or ≥10 mm Hg pressure reduction from baseline) or blood pressure control (defined as <140/90 mm Hg), plasma renin activity and concentration, safety and tolerability	Primary: All three doses investigated provided significantly greater reductions in mean sitting DBP from baseline compared to placebo (all *P*<0.0001). The mean sitting DBP reductions were 10.3 mm Hg with 150 mg, 11.1 mm Hg with 300 mg and 12.5 mm Hg with 600 mg compared to 4.9 mm Hg with placebo. Secondary: All three doses provided significantly greater reductions in mean sitting SBP from baseline compared to placebo (all *P*<0.0001). The mean sitting SBP reductions were 13.0 mm Hg with 150 mg, 14.7 mm Hg with 300 mg and 15.8 mm Hg with 600 mg compared to 3.8 mm Hg with placebo. Reduction in the 24-hour ABPM was significantly greater in all doses of aliskiren compared to placebo (n=216; all *P*<0.0001). Reductions in mean ambulatory DBP and SBP were consistent across the 24-hour dosing interval with all aliskiren doses. The proportion of patients achieving a successful treatment response was 59.3% with aliskiren 150 mg, 63.3% with 300 mg and 69.3% with 600 mg compared to 36.2% with placebo (all *P*<0.0001). The proportion of patients achieving blood pressure control was 35.9% with 150 mg, 41.6% with 300 mg and 46.4% with 600 mg compared to 20.3% with placebo (all *P*<0.0001). Plasma renin activity decreased 79.5% with 150 mg, 81.1% with 300 mg and 75.0% with 600 mg compared to an increase of 19.5% with placebo (*P* values not reported). Aliskiren treatment for 8 weeks resulted in dose-dependent increases from baseline in renin concentrations (51.5%, 101.6%, and 228.5% for 150, 300 and 600 mg, respectively; *P* values not reported). In the placebo group, renin concentrations were almost unchanged.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In general, aliskiren was well tolerated. The incidence of adverse events with aliskiren 150, 300 and 600 mg was 40.1%, 46.7% and 52.4%, respectively, compared with 43.0% for placebo. The incidence of diarrhea was significantly higher with aliskiren 600 mg (11.4%; *P*<0.0001) compared to aliskiren 300 mg (1.8%), aliskiren 150 mg (1.2%) and placebo (1.2%).
Kushiro et al[16] Aliskiren 75, 150 or 300 mg QD vs placebo	DB, MC, PC, PG, RCT Japanese men and women between the ages of 20 and 80 years with essential hypertension (mean sitting DBP of ≥90 mm Hg and <110 mm Hg during the run-in period and ≥95 mm Hg and <110 mm Hg at baseline)	N=455 8 weeks (active treatment)	Primary: Change in mean sitting DBP Secondary: Change in mean trough sitting SBP, proportion of patients responding to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm Hg decrease in mean sitting DBP from baseline), dose-response relationship, safety	Primary: All three aliskiren doses provided significantly greater reductions in mean sitting DBP from baseline compared to placebo. The placebo-corrected reductions in mean sitting DBP were 4.0 mm Hg with 75 mg aliskiren, 4.5 mm Hg with 150 mg and 7.5 mm Hg with 300 mg (all *P*<0.0005). Secondary: The mean sitting SBP reductions were significantly lower with all aliskiren doses when compared to placebo. The placebo-corrected reductions in mean sitting SBP were 5.7 mm Hg with 75 mg aliskiren, 5.9 mm Hg with 150 mg and 11.2 mm Hg with 300 mg (all *P*<0.001). The proportion of responders at study end point was 47.8% with aliskiren 75 mg, 48.2% with 150 mg and 63.7% with 300 mg compared to 27.8% with placebo (all *P*<0.005). Dose-response analysis showed that the relationship between reductions in mean sitting DBP and SBP and aliskiren dose was almost linear. However, further analyses revealed that a pattern of similar reductions with aliskiren 75 and 150 mg and greater reductions with aliskiren 300 mg was a better fit for both mean sitting DBP and SBP. The incidence of drug-related adverse events was comparable between aliskiren (53%-55%) and placebo (50%). There was no evidence of a dose-dependent increase in the incidence of all-causality adverse events at the aliskiren doses evaluated in this study.
Villamil et al[17] Aliskiren 75, 150 or 300 mg QD	DB, MC, PC, PG, RCT, factorial design	N=2,776 8 weeks	Primary: Compare aliskiren to placebo on change in mean sitting DBP,	Primary: Aliskiren monotherapy significantly reduced mean sitting DBP (*P*=0.0002; overall Dunnett's test) and the reductions were dose related. Although pairwise comparisons indicated that all 3 doses of aliskiren were statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs HCTZ 6.25, 12.5 or 25 mg QD vs aliskiren and HCTZ (every dose combination except aliskiren 300 mg and HCTZ 6.25 mg) QD vs placebo	Men and women ≥18 years with mild-to-moderate essential hypertension (mean sitting DBP 95-109 mm Hg)		compare aliskiren plus HCTZ to individual components on change in mean sitting DBP Secondary: Same as primary but mean sitting SBP, dose-response efficacy for all treatment groups, proportion achieving a successful response (DBP <90 mm Hg or ≥10 mm Hg), proportion achieving blood pressure control (<140/90 mm Hg), plasma renin activity, renin concentrations, safety	more effective than placebo, after adjusting for multiple comparisons, only the aliskiren 150 and 300 mg doses were more effective than placebo (*P*=0.09 for aliskiren 75 mg). HCTZ monotherapy significantly reduced DBP from baseline (all *P*<0.01 vs placebo), although no linear dose relationship was observed. All combinations were more effective than placebo (*P*<0.0001) with reductions in DBP ranging from 10.4 to 14.3 mm Hg. Most combination regimens were more effective than monotherapy with the individual components (exceptions were aliskiren 150 mg plus HCTZ 6.25 mg vs monotherapy, and aliskiren 75 mg plus HCTZ 12.5 vs HCTZ monotherapy). Secondary: After 8 weeks of therapy, aliskiren 150 and 300 mg regimens (both *P*<0.0001) were more effective than placebo in lowering mean sitting SBP, but the 75 mg dose was not (*P*=0.151). Combination therapy was consistently more effective in reducing SBP than monotherapy with the individual components, with the exception of aliskiren 75 mg plus HCTZ 12.5 vs HCTZ monotherapy. Reductions in SBP with combination therapy ranged from 14.3 to 21.2 mm Hg. Blood pressure reductions were related to the doses of both aliskiren and HCTZ. Responder rates were significantly higher with aliskiren 300 mg (63.9%; *P*=0.0005), HCTZ 12.5 and 25 mg (60.6% and 59.0%, respectively; both *P*<0.02) and all combination doses (58.4% to 80.6%; all *P*<0.05) than placebo (45.8%). Responder rates for all combinations of aliskiren plus HCTZ 25 mg, and aliskiren 300 mg plus HCTZ 12.5 mg were higher than both monotherapies (*P*<0.05), while aliskiren 75 mg plus HCTZ 12.5 mg and aliskiren 150 mg plus HCTZ 12.5 mg were more effective than their respective aliskiren monotherapies (*P*<0.05). In the aliskiren and HCTZ monotherapy groups, only aliskiren 300 mg led to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				statistically significantly greater control rates than placebo (46.7% vs 28.1%; *P*=0.0001). Control rates for all combinations, with the exception of aliskiren 75 mg plus HCTZ 6.25 mg, were higher than placebo (all *P*<0.02). There was a trend towards improved control rates with combination therapy (37.4% to 59.5%) compared to aliskiren monotherapy (29.0% to 46.7%) or HCTZ monotherapy (32.5% to 37.8%). Combinations utilizing the higher doses of one or both drugs (aliskiren 75-300 mg with HCTZ 25 mg or aliskiren 150-300 mg with HCTZ 12.5 mg) yielded control rates that were significantly higher than monotherapy with either component. While all doses of aliskiren decreased plasma renin activity and all doses of HCTZ increased plasma renin activity, combination therapy resulted in decreased plasma renin activity of 46.1% to 63.5%. Renin concentrations increased in all monotherapy and combination regimens with the exception of HCTZ 6.25 and 12.5 mg. All active treatments were well tolerated with 37.3% to 39.2% of patients experiencing adverse events with aliskiren monotherapy, 38.7% to 42.0% with HCTZ monotherapy, 34.6% to 45.3% with aliskiren plus HCTZ, and 44% with placebo (no *P* values reported). Hypokalemia (serum potassium <3.5 mmol/L) occurred with the highest frequency with HCTZ 12.5 and 25 mg (3.9% and 5.2%, respectively). When administered in combination with aliskiren, the frequency of hypokalemia was 0.7% to 2.0% with HCTZ 12.5 mg and 2.2% to 3.4% with HCTZ 25 mg.
Strasser et al[18] Aliskiren 150 to 300 mg QD (n=125) vs lisinopril 20 to 40 mg QD (n=58) HCTZ may be added to aliskiren 300 mg or	AC, DB, DD, MC, PG, RCT Men and women with uncomplicated severe hypertension (mean sitting DBP 105-119 mm Hg)	N=183 8 weeks	Primary: Safety Secondary: Change in mean sitting DBP and SBP, percentage of responders	Primary: Both active treatments were well tolerated with an incidence of adverse events of 32.8% for aliskiren and 29.3% for lisinopril. The proportion of patients discontinuing treatment due to adverse events was 3.2% for aliskiren and 3.4% for lisinopril. The most frequently reported adverse events in both groups were headache, nasopharyngitis and dizziness (no *P* values were reported for this endpoint). Secondary: Aliskiren showed similar reductions from baseline to lisinopril in mean sitting DBP (–18.5 vs –20.1 mm Hg) and SBP (–20.0 and –22.3 mm Hg; no *P* values were reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lisinopril 40 mg if additional blood pressure control was required. The study did not specifically analyze the effects of HCTZ on either treatment regimen.				Responder rates were 81.5% with aliskiren and 87.9% with lisinopril. Approximately half of patients required the addition of HCTZ to achieve blood pressure control (53.6% for aliskiren and 44.8% for lisinopril; no *P* values were reported).
Anderson et al[19] Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD The addition of HCTZ was permitted at week 12 in patients not achieving adequate blood pressure control (<140/90 mm Hg). The study did not specifically analyze the effects of HCTZ on either treatment regimen.	AC, DB, MC, PC, RCT Men and women ≥18 years with essential hypertension (mean sitting DBP 90-109 mm Hg)	N=842 26 weeks (active treatment)	Primary: Change in mean sitting DBP at week 26 Secondary: Change in mean sitting SBP at week 26, change in mean sitting SBP and DBP at week 6 and 12 (comparing aliskiren and ramipril monotherapy), proportion achieving blood pressure control (<140/90 mm Hg), proportion achieving SBP control (<140 mm Hg), safety	Primary: Reductions in mean sitting DBP at week 26 were significantly greater with aliskiren-based therapies (–13.2 mm Hg) than with ramipril-based therapies (–12.0 mm Hg; *P*=0.0250). Secondary: Reductions in mean sitting SBP at week 26 were significantly greater with aliskiren-based therapies (–17.9 mm Hg) than with ramipril-based therapies (–15.2 mm Hg; *P*=0.0036). Mean changes in sitting SBP were significantly greater with aliskiren (–12.9 and –14.0 mm Hg, respectively) than ramipril (–10.5 and –11.3, respectively) at weeks 6 and 12 (*P*=0.0041 and *P*=0.0027, respectively). Mean changes in sitting DBP were not significantly greater with aliskiren (–10.5 and –11.3 mm Hg, respectively) than ramipril (–9.5 and –9.7, respectively) at week 6 but were significantly greater at week 12 (*P*=0.0689 and *P*=0.0056, respectively). The proportion of patients achieving overall blood pressure control <140/90 mm Hg was significantly higher with aliskiren-based therapy (61.4%) than with ramipril-based therapy (53.1%; *P*=0.0205) at week 26. Also, the proportion of patients achieving SBP control <140 mm Hg was significantly higher with aliskiren-based therapy (72.5%) than with ramipril-based therapy (64.1%; *P*=0.0075) at week 26. The majority of adverse events reported during the active treatment period were mild or moderate in intensity and transient. Most events occurred at a similar incidence in the 2 groups with the exception of cough which was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				considered treatment-related in 5.5% of patients receiving ramipril versus 2.1% of patients receiving aliskiren (no *P* values reported).
Obrien et al[20] Aliskiren 150 mg QD for 3 weeks, if ABPM remained ≥135/85 mm Hg, HCTZ 25 mg QD was added for an additional 3 weeks (n=23 with 17 patients receiving HCTZ) vs irbesartan 150 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks (n=23) vs ramipril 5 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks (n=21)	3 OL studies Men and women 18-80 years with ambulatory SBP ≥ 140 and ≤ 180 mm Hg without treatment	N=67 6-9 weeks	Primary: Change in daytime systolic ABPM with combination therapy compared with monotherapy Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart rates, plasma renin activity	Primary: Aliskiren coadministered with HCTZ (*P*=0.0007) or ramipril (*P*=0.03) led to significantly greater reductions in daytime systolic ABPM compared to monotherapy. There was a trend for a reduction in daytime systolic ABPM with the addition of aliskiren to irbesartan; however, this trend was not statistically significant (*P* value not reported). Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (*P*=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (*P*=0.06 and *P*=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen. Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (all *P*<0.05). No changes in heart rate were observed with either irbesartan regimen. Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (*P*<0.05) but not aliskiren 75 mg (*P* value not reported) to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and diastolic ABPM (all *P*<0.05). No changes in heart rate were observed with either ramipril regimen. Aliskiren alone significantly inhibited plasma renin activity by 65% (*P*<0.0001), while ramipril and irbesartan monotherapy increased renin activity by 90% and 175%, respectively. When aliskiren was coadministered with HCTZ, ramipril or irbesartan, plasma renin activity remained similar to baseline levels or decreased.
Jordan et al[21] Aliskiren 150 mg QD	DB, DD, MC, PG, RCT Obese men and	N=489 16 weeks (4 weeks of	Primary: Change in mean sitting DBP with aliskiren 300 mg plus	Primary: Aliskiren 300 mg added to HCTZ 25 mg significantly reduced mean sitting DBP compared with HCTZ alone at week 8 (mean difference, –4.0; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amlodipine 5 mg QD vs irbesartan 150 mg QD vs placebo After 4 weeks, doses of aliskiren, irbesartan and amlodipine were doubled and treatment was continued for an additional 8 weeks. All patients continued to received HCTZ 25 mg QD.	women (BMI ≥ 30 kg/m^2) ≥ 18 years with essential hypertension (mean sitting DBP 95-109 mm Hg and SBP <180 mm Hg) who had not responded to 4 weeks of treatment with HCTZ 25 mg	HCTZ monotherapy and 12 weeks of combination therapy)	HCTZ vs HCTZ alone at 8 weeks Secondary: Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of responders (mean sitting DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), proportion of patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), plasma renin activity, safety and tolerability	Secondary: Aliskiren 300 mg added to HCTZ caused numerically larger reductions in mean sitting DBP and SBP compared with amlodipine 10 mg plus HCTZ and irbesartan 300 mg plus HCTZ at week 8, but there were no statistically significant differences between treatment groups (*P*>0.05). Responder rates were significantly higher with aliskiren plus HCTZ than HCTZ alone at week 8 (*P*=0.0193) and week 12 (*P*=0.004) but comparable to responder rates observed with amlodipine plus HCTZ (*P*>0.05) and irbesartan plus HCTZ (*P*>0.05). The proportion of patients achieving blood pressure control was significantly higher with aliskiren plus HCTZ than HCTZ alone at week 8 (*P*=0.0005) and week 12 (*P*=0.0001) but not statistically different than amlodipine plus HCTZ (*P*>0.05) and irbesartan plus HCTZ (*P*>0.05). Plasma renin activity significantly increased (*P*<0.05) during 4 weeks of HCTZ monotherapy. Combination with aliskiren neutralized this increase and led to an overall significant reduction in plasma renin activity compared with pretreatment baseline (*P*<0.05) whereas amlodipine and irbesartan led to further significant increases (*P*<0.05). All of the study treatments were generally well tolerated. Amlodipine plus HCTZ (45.2%) was associated with a higher incidence of adverse events than the other treatment groups (36.1% to 39.3%; no *P* values reported), largely due to a higher rate of peripheral edema (11.1% vs 0.8% to 1.6%; no *P* values reported).
Gradman et al[22] Aliskiren 150, 300, or 600 mg QD vs irbesartan 150 mg QD	DB, MC, PC, PG, RCT Men and women, age 18 years or older, with mild-to-moderate essential hypertension (mean	N=652 13 weeks (8 weeks active treatment)	Primary: Change in mean sitting DBP and SBP Secondary: Proportion of patients achieving blood pressure control	Primary: Decreases in mean sitting DBP at 8 weeks were significantly greater with all doses of aliskiren compared to placebo (*P*<0.001). The least-squares mean reductions in trough DBP for aliskiren 150, 300 and 600 mg were 9.3, 11.8, and 11.5 mm Hg, respectively, versus 6.3 mm Hg for placebo. Decreases in mean sitting SBP at 8 weeks were significantly greater with all doses of aliskiren compared to placebo (*P*<0.001). The least-squares mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	sitting DBP ≥ 95 mm Hg and <110 mm Hg)		(<140/90 mm Hg), safety	reductions in trough SBP for aliskiren 150, 300 and 600 mg were 11.4, 15.8, and 15.7 mm Hg, respectively, versus 5.3 mm Hg for placebo. The antihypertensive effect of aliskiren 150 mg was comparable to irbesartan 150 mg with reductions of 8.9 and 12.5 mm Hg for mean sitting DBP and SBP, respectively. Aliskiren 300 and 600 mg produced significantly greater mean sitting DBP reductions than irbesartan 150 mg (*P*<0.05). While the reductions in mean sitting SBP were greater with aliskiren 300 and 600 mg than irbesartan 150 mg, these differences were not statistically significant (*P* values not reported). Secondary: The percentage of patients achieving blood pressure control was significantly greater with all doses of aliskiren (37.8%-150 mg, 50.0%-300 mg, 45.7%-600 mg) and irbesartan (33.8%) compared to placebo (20.8%; *P*<0.05). More patients on aliskiren 300 and 600 mg achieved blood pressure control compared to irbesartan (*P*<0.05). Drug-related adverse events for both aliskiren and irbesartan were comparable to placebo and the most commonly reported adverse events were headache, dizziness, and diarrhea. The number of patients discontinuing therapy was similar in all groups.
Stanton et al[23] Aliskiren 37.5, 75, 150, or 300 mg QD vs losartan 100 mg QD	AC, DB, MC, PG, RCT Men and women 21 to 70 years of age with mild-to-moderate hypertension (SBP ≥ 140 mm Hg)	N=226 4 weeks	Primary: Change in daytime ambulatory SBP Secondary: Changes in clinic SBP and DBP, plasma renin activity, plasma aliskiren levels, adverse events	Primary: A clear dose-dependent reduction in daytime ambulatory SBP was observed with increasing aliskiren doses (with mean changes of –0.40 mm Hg with aliskiren 37.5 mg, –5.3 mm Hg with aliskiren 75 mg, –8.0 mm Hg with aliskiren 150 mg, and –11.0 mm Hg with aliskiren 300 mg; *P*=0.0002). The change in daytime SBP with losartan 100 mg (–10.9 mm Hg) was significantly different than aliskiren 37.5 mg but not the other higher aliskiren dosages (*P* values not reported). Secondary: Clinic SBP and DBP, both in the sitting and standing positions, decreased with aliskiren in a dose-dependent manner, whereas heart rate was unaltered. The decreases in clinic blood pressures were similar for losartan 100 mg and aliskiren 150 and 300 mg.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Dose-dependent reductions in plasma renin activity were also observed (median change –55%, –60%, –77%, and –83% with 37.5, 75, 150 and 300 mg aliskiren, respectively; *P*=0.0008). By contrast, plasma renin activity increased by 110% with losartan 100 mg. Rate of adverse events was 22% with aliskiren 37.5 mg, 35% with aliskiren 75 mg, 25% with aliskiren 150 mg, 23% with aliskiren 300 mg, and 32% with losartan 100 mg (no *P* value reported). There was no increase in the number of adverse events when increasing the dose of aliskiren.
Parving et al[24] AVOID Losartan 100 mg daily plus aliskiren 150 mg daily for 3 months then 300 mg for an additional 3 months vs losartan 100 mg plus placebo	DB, MC, PC, RCT Hypertensive patients who were 18 to 85 years of age who had type 2 diabetes and nephropathy	N=599 6 months	Primary: Reduction in albumin:creatinine ratio at 6 months Secondary: Blood pressure reductions, adverse events	Primary: Treatment with aliskiren 300 mg daily as compared with placebo reduced the mean urinary albumin: creatinine ratio by 20% (95% CI, 9 to 30; *P*<0.001), with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared with 12.5% of those who received placebo (*P*<0.001). Secondary: A small difference in blood pressure was seen between the treatment groups by the end of the study period with SBP and DBP pressures 2 and 1 mm Hg lower, respectively, in the aliskiren group (*P*=0.07 and *P*=0.08, respectively). The total numbers of adverse and serious adverse events were similar in the groups.
Oparil et al[25] Aliskiren 150 mg QD vs valsartan 160 mg QD vs aliskiren 150 mg plus valsartan 160 mg	DB, MC, PC, PG, RCT Men and women aged 18 years or over with stage 1-2 essential hypertension (mean sitting DBP 95-109 mm Hg and 8-hour ambulatory DBP ≥90 mm Hg)	N=1,797 8 weeks (4 weeks with forced titration to double the dose to the maximum recommended dose for another 4 weeks)	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, proportion of patients achieving a successful response to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm	Primary: At week 8, the combination of aliskiren 300 mg plus valsartan 320 mg lowered mean sitting DBP from baseline by 12.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (–9.0 mm Hg; *P*<0.0001), valsartan 320 mg (–9.7 mm Hg; *P*<0.0001) or with placebo (–4.1 mm Hg; *P*<0.0001). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting DBP than did placebo at week 8 (all *P*<0.0001). Secondary: At week 8, the combination of aliskiren 300 mg plus valsartan 320 mg lowered mean sitting SBP from baseline by 17.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (–13.0 mm Hg; *P*<0.0001),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			Hg reduction from baseline) or achieving blood pressure control (mean sitting SBP/DBP <140/90 mm Hg), change in 24-hour ABPM, change in biomarkers, safety	valsartan 320 mg (–12.8 mm Hg; *P*<0.0001) or with placebo (–4.6 mm Hg; *P*<0.0001). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting SBP than did placebo at week 8 end point (all *P*<0.0001). The proportion of patients achieving a successful response to treatment at week 8 was significantly higher with the combination of aliskiren and valsartan (66%) than with aliskiren alone (53%; *P*=0.0003) or valsartan alone (55%; *P*=0.0010). All active treatments were associated with significantly greater responder rates than placebo (30%; all *P*<0.0001). The proportion of patients achieving blood pressure control was significantly greater in the combination group (49%) than in the aliskiren (37%; *P*=0.0005) or valsartan (34%; *P*<0.0001) monotherapy groups. All active treatments were associated with significantly greater control rates than placebo (16%; all *P*<0.0001). The combination of aliskiren and valsartan was significantly more effective in lowering mean 24-hour ambulatory SBP and DBP than was either agent alone (all *P*<0.0001). The greater reductions in ambulatory blood pressure with aliskiren plus valsartan were maintained throughout the entire 24-hour dosing interval. Aliskiren plus valsartan (*P*<0.0001) and monotherapy with aliskiren (*P*<0.0001) or valsartan (*P*=0.0002) provided significant increases in plasma renin concentrations versus placebo. Increases in plasma renin concentrations were significantly greater for the combination than aliskiren (*P*=0.0014) or valsartan (*P*<0.0001) monotherapy. Valsartan monotherapy produced significantly greater increases in plasma renin activity than placebo (160% vs 18%; *P*=0.0003). By contrast, aliskiren alone significantly reduced plasma renin activity by 73% (*P*<0.0001 vs placebo), while the combination of aliskiren plus valsartan led to a reduction in plasma renin activity of 44% (*P*<0.0001 vs placebo). The combination of aliskiren and valsartan (–31%; *P*<0.0001) and valsartan

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				monotherapy (–25%; *P*=0.0007) provided significantly greater reductions in plasma aldosterone concentration than did placebo (+7%), while aliskiren monotherapy had no significant effect (–5.9%; *P*=0.1059). Rates of adverse events and laboratory abnormalities were similar in all groups.
Pool et al[26] Aliskiren 75, 150, or 300 mg QD vs valsartan 80, 160 or 320 mg vs aliskiren 75, 150 or 300 mg plus valsartan 80, 160 mg and 320 mg, respectively (separate entities) vs valsartan 160 mg plus HCTZ 12.5 mg (fixed-dose combination) vs placebo	DB, MC, PC, PG, RCT Men and women ≥18 years with mild-to-moderate essential hypertension (mean sitting DBP ≥95 mm Hg after a 3- to 4-week single-blind placebo run-in period)	N=1,123 8 weeks	Primary: Change in mean sitting DBP with aliskiren monotherapy compared to placebo Secondary: Change in mean sitting SBP, efficacy of aliskiren and valsartan combinations compared to the respective monotherapies and valsartan plus hydrochlorothiazide combination therapy, safety	Primary: Aliskiren 300 mg significantly (*P*<0.0001) lowered mean sitting DBP compared with placebo. Reductions in mean sitting DBP for aliskiren 75 and 150 mg compared to placebo failed to reach statistical significance (*P*=0.052 and *P*=0.051, respectively). Secondary: Aliskiren 300 mg significantly (*P*<0.0001) lowered mean sitting SBP compared with placebo. A statistically significant linear dose relationship was observed for the effect of aliskiren (75 to 300 mg) on mean sitting DBP (*P*=0.0002) and mean sitting SBP (*P*=0.0005). The effects of aliskiren monotherapy on mean sitting DBP and SBP across the 75 to 300 mg dose range were similar to the effects of valsartan 80 to 320 mg. Coadministration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone. Reductions in mean sitting DBP and SBP obtained with aliskiren 150 mg plus valsartan 160 mg and aliskiren 300 mg plus valsartan 320 mg were not significantly different from those observed with valsartan 160 mg plus HCTZ 12.5 mg. Responder rates were significantly greater than placebo for all 3 aliskiren monotherapy groups and for all aliskiren plus valsartan combinations. The proportion of responders with aliskiren 75 mg plus valsartan 80 mg was significantly greater than either component monotherapy (*P*<0.05). There was no significant difference between the proportion of responders to aliskiren 150 mg plus valsartan 160 mg or aliskiren 300 mg plus valsartan 320 mg compared with valsartan 160 mg plus HCTZ 12.5 mg.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Control rates were higher with aliskiren 300 mg compared with placebo and with valsartan 160 mg plus HCTZ 12.5 mg compared with aliskiren 150 mg plus valsartan 160 mg, but there were no significant differences between aliskiren plus valsartan combinations and the respective monotherapies. Aliskiren and valsartan were generally well tolerated either as monotherapy or in combination. The overall incidence of adverse events and rate of discontinuations because of adverse events were similar to placebo in all active treatment groups.

Drug regimen abbreviations: HCTZ=hydrochlorothiazide, QD=once daily
Study abbreviations: AC=active-controlled, BMI=body mass index, DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, BMI=body mass index, DBP=diastolic blood pressure, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity Renin Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
aliskiren	tablet	Tekturna®	$$$	N/A

No generic products are available in this class.
N/A=not available.

X. Conclusions

Aliskiren is the only single entity renin inhibitor marketed in the United States and it is not available generically. Aliskiren is Food and Drug Administration approved for the treatment of hypertension, either alone or in combination with other antihypertensive agents. Clinical trials have demonstrated that aliskiren 150 to 300 mg once daily is significantly more effective than placebo in lowering both systolic and diastolic blood pressures in men and women with mild-to-moderate essential hypertension.[15,16] Doses above 300 mg did not give an increased blood pressure response but increased the rate of diarrhea.[2,15] Aliskiren was associated with an increase in plasma renin concentrations but a decrease in plasma renin activity.[15]

Limited comparative trials of aliskiren with other antihypertensive agents, including the angiotensin-converting enzyme (ACE) inhibitors[18] and angiotensin receptor blockers (ARBs), [21,22,24] have generally demonstrated similar efficacy when administered in comparable doses. In general, the incidence of side effects was also comparable. One study reported better efficacy with aliskiren than ramipril, and a higher incidence of cough with ramipril (5.5%) than aliskiren (2.1%).[19]

Aliskiren has also been studied in combination with other antihypertensive agents. When given concurrently with hydrochlorothiazide,[17,20,21] an ACE inhibitor,[20] or an ARB,[20,25,26] in general the combination therapies produced more pronounced decreases in blood pressure and better control than monotherapy with the individual components, without a significant increase in adverse events. While plasma renin activity increased during hydrochlorothiazide, ACE inhibitor and ARB monotherapy, plasma renin activity remained similar to baseline or decreased when aliskiren was coadministered.[17,20,25] When administered to hypertensive patients with diabetic nephropathy who were already receiving losartan, aliskiren reduced the mean urinary albumin: creatinine ratio by 20% compared to placebo with only small differences in blood pressure.[24] Additional studies are needed to determine the role of aliskiren in hypertensive patients with diabetic nephropathy.

Overall, aliskiren appears to be well tolerated with clinical trials reporting adverse events similar to placebo at doses up to 300 mg daily.[5] Like other drugs that act directly on the renin-angiotensin-aldosterone system (RAAS), aliskiren carries a black box warning against use during pregnancy.[2]

To date, there are no long-term trials evaluating the safety and efficacy of aliskiren or determining whether aliskiren improves clinical outcomes. In addition, the role of renin inhibitors has not been addressed by the national and international consensus guidelines for the management of hypertension.

At this time, there is insufficient data to conclude that the single entity renin inhibitors offer significant clinical advantage over other alternatives in general use. Therefore all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over the other alternatives in general use.

XI. Recommendations

No brand single entity renin inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Renin Inhibitors
Combination Products
AHFS Class 243240
September 10, 2008

I. Overview

Tekturna HCT® is the only combination renin inhibitor available in the United States (US). It was approved by the Food and Drug Administration (FDA) on January 18, 2008 for the treatment of hypertension.[1,2] Tekturna HCT® contains aliskiren, a direct renin inhibitor, in fixed-dose combinations with hydrochlorothiazide, a diuretic.

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[3] Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is the first and rate-limiting step of the RAAS.[2-5] Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II can increase blood pressure by direct vasoconstriction and stimulation of catecholamine release. In addition, angiotensin II induces aldosterone secretion, leading to sodium and fluid retention.[5] Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy, inflammation, remodeling, and thrombosis. Through a negative feedback mechanism, angiotensin II inhibits renin release.[2] As a direct renin inhibitor, aliskiren reduces angiotensin I, angiotensin II and aldosterone levels by binding to renin with high affinity in the plasma.[4,5] All drugs that inhibit RAAS, including aliskiren, can suppress the negative feedback loop and cause a compensatory increase in plasma renin concentrations. Aliskiren blocks the effects of increased renin levels.[2] The effects of aliskiren on other components of the RAAS are not known.

Hydrochlorothiazide, a thiazide diuretic, increases the excretion of sodium and chloride by inhibiting their reabsorption in the ascending loop of Henle and the early distal tubules of the kidney.[6] Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, which increases plasma renin activity, aldosterone secretion and subsequently potassium excretion in the urine.[2] The exact antihypertensive mechanism of the thiazide diuretics is unknown, although sodium depletion appears to be an important factor.[6]

The combination renin inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Combination Renin Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
aliskiren and hydrochlorothiazide	tablet	Tekturna HCT®	none

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

As noted above, Tekturna HCT® was the first combination renin inhibitor marketed in the United States and it was Food and Drug Administration approved in January 2008 for the management of hypertension.[1] Table 2 outlines the current national and international treatment guidelines for the pharmacologic management of hypertension. At this time, none of these guidelines have incorporated recommendations regarding the use of renin inhibitors, either the single entity agents or fixed-dose combination products. General recommendations regarding the use of combination therapy, particularly with diuretics, has been included in the table. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines for the Combination Renin Inhibitors

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood	• The use of renin inhibitors was not addressed in this guideline.

Clinical Guideline	Recommendation(s)
Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)**[7]	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with two antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • The use of fixed-dose combination products was not addressed in this guideline.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[8]	• The use of renin inhibitors was not addressed in this guideline. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • The use of fixed-dose combination products was not addressed in this guideline.
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[9]	• The use of renin inhibitors was not addressed in this guideline. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, and the combination is likely to be well tolerated.
Treatment Guidelines From the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[10]	• The use of renin inhibitors was not addressed in this guideline. • Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment. • The use of fixed-dose combination products was not addressed in this guideline.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[11]	• The use of renin inhibitors was not addressed in this guideline. • Initial therapy in patients ≥55 years should be a calcium-channel blocking agent (CCB) or a thiazide diuretic, and in patients <55 years initial therapy should be an angiotensin-converting enzyme (ACE) inhibitor. If a second medication is required and the initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • The use of fixed-dose combination products was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes–2008**[12]	• The use of renin inhibitors was not addressed in this guideline. • The initial drug therapy regimen should include an ACE inhibitor or an angiotensin receptor blocker (ARB). If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is >50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73m^2. (Note: Tekturna

Clinical Guideline	Recommendation(s)
	HCT® is not recommended in patients with a creatinine clearance of ≤30 mL/min.[2]) • Multiple drug therapy is generally required to achieve blood pressure goals. • The use of fixed-dose combination products was not addressed in this guideline.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[13]	• The use of renin inhibitors was not addressed in this guideline. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB or ARB plus diuretic. • The use of fixed-dose combination products was not addressed in this guideline.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[14]	• The use of renin inhibitors was not addressed in this guideline. • All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30mL/min/1.73m^2. (Note: Tekturna HCT® is not recommended in patients with a creatinine clearance of ≤30 mL/min.[2]) Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence.

III. Indications

FDA-approved indications for the combination renin inhibitors are noted in Table 3. While this agent 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 Combination Renin Inhibitors[2]

Drug	Indication
Aliskiren and hydrochlorothiazide	Treatment of hypertension; this fixed-dose combination is not indicated for initial therapy

IV. Pharmacokinetics

The pharmacokinetic parameters for the combination renin inhibitors are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Combination Renin Inhibitors[2,15,16]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination	Half-Life (hours)
Aliskiren	2.5	49.5	Liver, extent unknown*	Unknown	25% unchanged in the urine	24
Hydrochlorothiazide	50-75	40-68	Not appreciably metabolized	Not reported	Urine	6-15

*In vitro studies indicate that the major enzyme responsible for aliskiren metabolism appears to be CYP3A4.

V. Drug Interactions

Significant drug interactions reported with the combination renin inhibitors are summarized in Table 5.

Table 5. Significant Drug-Drug Interactions with the Combination Renin Inhibitors[2,15,16]

Drug	Significance Level	Interaction	Mechanism
Hydrochlorothiazide	1	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Hydrochlorothiazide	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Aliskiren	2	Angiotensin-converting enzyme (ACE) inhibitors	Aliskiren has been associated with infrequent increases in serum potassium >5.5 meq/L (0.9% vs 0.6% with placebo). When aliskiren was used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Use caution when aliskiren is given concomitantly with ACE inhibitors. Routine monitoring of electrolytes and renal function is indicated in this population.
Aliskiren	2	Atorvastatin	Concurrent administration of aliskiren with atorvastatin (a CYP3A4 substrate) led to a 50% increase in aliskiren area under the curve (AUC) and maximum concentration (C_{max}) following multiple dosing. Caution is advised if aliskiren is administered concurrently with atorvastatin.
Aliskiren	2	Furosemide	Concurrent administration of aliskiren with furosemide resulted in decreases of 30% and 50% in furosemide AUC and C_{max}, respectively. Caution is advised if these agents are coadministered.
Aliskiren	2	Ketoconazole	Concurrent administration of aliskiren with ketoconazole (a CYP3A4 inhibitor) at 200 mg twice daily led to an 80% increase in plasma levels of aliskiren. Caution is advised if aliskiren is administered concurrently with ketoconazole.
Hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Hydrochlorothiazide	2	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Hydrochlorothiazide	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate carefully in small or intermittent doses.
Hydrochlorothiazide	2	Sulfonylureas (chlorpropamide,	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This

Drug	Significance Level	Interaction	Mechanism
		glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.
Aliskiren	Unknown*	Cyclosporine	Coadministration of 200 mg and 600 mg cyclosporine with 75 mg aliskiren resulted in 2.5 and 5 fold increases in C_{max} and AUC, respectively. Concomitant use of aliskiren with cyclosporine is not recommended.
Aliskiren	Unknown*	Irbesartan	Irbesartan reduced the maximum concentration of aliskiren by up to 50% after multiple dosing. The clinical significance of this interaction was not reported.

*The significance level was not reported.
Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the combination renin inhibitors are summarized in Table 6.

Table 6. Adverse Drug Events (%) Reported for the Combination Renin Inhibitors[2,16]

Adverse Event(s)	Aliskiren	Hydrochlorothiazide	Aliskiren and Hydrochlorothiazide (Tekturna HCT®)
Cardiovascular			
Hypotension	<1 (severe)	1-10	<1
Orthostatic hypotension	-	1-10	-
Central Nervous System			
Dizziness	✔	-	2
Fatigue	✔	-	-
Headache	✔	-	-
Seizure	<1	-	-
Vertigo	-	-	1
Dermatologic			
Alopecia	-	<1	-
Erythema multiforme (including Stevens-Johnson syndrome)	-	<1	-
Exfoliative dermatitis (including toxic epidermal necrolysis)	-	<1	-
Photosensitivity	-	1-10	-
Rash	1	-	-
Gastrointestinal/Hepatic			
Abdominal pain	<1	-	-
Alanine aminotransaminase increased	-	-	1
Anorexia	-	1-10	-
Diarrhea	1-2	-	2
Dyspepsia	<1	-	-
Epigastric distress	-	1-10	-
Gastroesophageal reflux	<1	-	-
Hepatic function impairment	-	<1	-
Pancreatitis	-	<1	-
Hematologic			
Agranulocytosis	-	<1	-

Adverse Event(s)	Aliskiren	Hydrochlorothiazide	Aliskiren and Hydrochlorothiazide (Tekturna HCT®)
Anemia	<1	-	-
Aplastic anemia	-	<1	-
Hematocrit decreased	<1	-	<1
Hemoglobin decreased	<1	-	<1
Hemolytic anemia	-	<1	-
Leukopenia	-	<1	-
Thrombocytopenia	-	<1	-
Hypersensitivity			
Allergic myocarditis	-	<1	-
Allergic reactions (including anaphylactic shock)	-	<1	-
Angioedema	<1	-	-
Rash	1	-	-
Metabolic			
Gout	<1	-	✔
Hypercalcemia	-	<1	-
Hyperkalemia	1*	-	1
Hypokalemia	-	1-10	2
Uric acid increased	<1	-	2
Musculoskeletal			
Arthralgia	-	-	1
Asthenia	-	-	1
Creatine kinase increased (>300%)	1	-	-
Myositis	<1	-	-
Rhabdomyolysis	<1	-	-
Renal			
Blood urea nitrogen increased	≤7	-	12
Interstitial nephritis	-	<1	-
Renal failure	-	<1	-
Renal stone formation	<1	-	✔
Serum creatinine increased	≤7	-	1
Respiratory			
Cough	1†	-	1
Eosinophilic pneumonitis	-	<1	-
Influenza	-	-	2
Nasopharyngitis	✔	-	-
Respiratory distress	-	<1	-
Upper respiratory infection	✔	-	-
Other			
Back pain	✔	-	-
Edema (face, hands, or whole body)	<1	-	<1
Periorbital edema	✔	-	-

✔ Percent not specified.
-Event not reported or incidence <1%.
*The incidence of hyperkalemia was 1% with monotherapy and 6% with concurrent angiotensin-converting enzyme (ACE) inhibitor therapy in patients with diabetes.
†In active-controlled trials with ramipril and lisinopril, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Table 7. Black Box Warning for the Combination Renin Inhibitors[2]

WARNING: AVOID USE IN PREGNANCY
When pregnancy is detected, discontinue Tekturna HCT® as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. [*See Warnings and Precautions*.]

VII. Dosing and Administration

The usual dosing regimens for combination renin inhibitors are summarized in Table 8.

Table 8. Usual Dosing for the Combination Renin Inhibitors[2]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Aliskiren and hydrochlorothiazide	Hypertension: Once-daily doses in order of increasing mean effect are aliskiren 150 mg-hydrochlorothiazide 12.5 mg, 150 mg-25 mg or 300 mg-12.5 mg and 300 mg-25 mg; regardless of the dose of the single agent, patients switched from monotherapy to the fixed-dose combination product will experience greater blood pressure reductions; if blood pressure remains uncontrolled after 2 to 4 weeks of therapy, the dose may be titrated up to a maximum of aliskiren 300 mg-hydrochlorothiazide 25 mg	Safety and efficacy in children have not been established.	Tablet: 150 mg-12.5 mg 150 mg-25 mg 300 mg-12.5 mg 300 mg-25 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the combination renin inhibitors are found in Table 9.

Table 9. Comparative Clinical Trials Using Combination Renin Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Villamil et al[17] Aliskiren 75, 150 or 300 mg QD vs HCTZ 6.25, 12.5 or 25 mg QD vs aliskiren and HCTZ (every dose combination except aliskiren 300 mg and HCTZ 6.25 mg) QD vs placebo	DB, MC, PC, PG, RCT, factorial design Men and women ≥18 years with mild-to-moderate essential hypertension (mean sitting DBP 95-109 mm Hg)	N=2,776 8 weeks	Primary: Compare aliskiren to placebo on change in mean sitting DBP, compare aliskiren plus HCTZ to individual components on change in mean sitting DBP Secondary: Same as primary but mean sitting SBP, dose-response efficacy for all treatment groups, proportion achieving a successful response (DBP <90 mm Hg or ≥10 mm Hg), proportion achieving blood pressure control (<140/90 mm Hg), plasma renin activity, renin concentrations, safety	Primary: Aliskiren monotherapy significantly reduced mean sitting DBP (*P*=0.0002; overall Dunnett's test) and the reductions were dose related. Although pairwise comparisons indicated that all 3 doses of aliskiren were statistically more effective than placebo, after adjusting for multiple comparisons, only the aliskiren 150 and 300 mg doses were more effective than placebo (*P*=0.09 for aliskiren 75 mg). HCTZ monotherapy significantly reduced DBP from baseline (all *P*<0.01 vs placebo), although no linear dose relationship was observed. All combinations were more effective than placebo (*P*<0.0001) with reductions in DBP ranging from 10.4 to 14.3 mm Hg. Most combination regimens were more effective than monotherapy with the individual components (exceptions were aliskiren 150 mg plus HCTZ 6.25 mg vs monotherapy, and aliskiren 75 mg plus HCTZ 12.5 vs HCTZ monotherapy). Secondary: After 8 weeks of therapy, aliskiren 150 and 300 mg regimens (both *P*<0.0001) were more effective than placebo in lowering mean sitting SBP, but the 75 mg dose was not (*P*=0.151). Combination therapy was consistently more effective in reducing SBP than monotherapy with the individual components, with the exception of aliskiren 75 mg plus HCTZ 12.5 vs HCTZ monotherapy. Reductions in SBP with combination therapy ranged from 14.3 to 21.2 mm Hg. Blood pressure reductions were related to the doses of both aliskiren and HCTZ.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Responder rates were significantly higher with aliskiren 300 mg (63.9%; *P*=0.0005), HCTZ 12.5 and 25 mg (60.6% and 59.0%, respectively; both *P*<0.02) and all combination doses (58.4% to 80.6%; all *P*<0.05) than placebo (45.8%). Responder rates for all combinations of aliskiren plus HCTZ 25 mg, and aliskiren 300 mg plus HCTZ 12.5 mg were higher than both monotherapies (*P*<0.05), while aliskiren 75 mg plus HCTZ 12.5 mg and aliskiren 150 mg plus HCTZ 12.5 mg were more effective than their respective aliskiren monotherapies (*P*<0.05). In the aliskiren and HCTZ monotherapy groups, only aliskiren 300 mg led to statistically significantly greater control rates than placebo (46.7% vs 28.1%; *P*=0.0001). Control rates for all combinations, with the exception of aliskiren 75 mg plus HCTZ 6.25 mg, were higher than placebo (all *P*<0.02). There was a trend towards improved control rates with combination therapy (37.4% to 59.5%) compared to aliskiren monotherapy (29.0% to 46.7%) or HCTZ monotherapy (32.5% to 37.8%). Combinations utilizing the higher doses of one or both drugs (aliskiren 75-300 mg with HCTZ 25 mg or aliskiren 150-300 mg with HCTZ 12.5 mg) yielded control rates that were significantly higher than monotherapy with either component. While all doses of aliskiren decreased plasma renin activity and all doses of HCTZ increased plasma renin activity, combination therapy resulted in decreased plasma renin activity of 46.1% to 63.5%. Renin concentrations increased in all monotherapy and combination regimens with the exception of HCTZ 6.25 and 12.5 mg. All active treatments were well tolerated with 37.3% to 39.2% of patients experiencing adverse events with aliskiren monotherapy, 38.7% to 42.0% with HCTZ monotherapy, 34.6% to 45.3% with aliskiren plus HCTZ, and 44% with placebo (no *P* values reported). Hypokalemia (serum potassium <3.5 mmol/L) occurred with the highest frequency with HCTZ 12.5 and 25 mg (3.9% and 5.2%, respectively). When administered in combination with aliskiren, the frequency of hypokalemia was 0.7% to 2.0% with HCTZ 12.5 mg and 2.2% to 3.4% with HCTZ 25 mg.
Strasser et al[18]	AC, DB, DD, MC,	N=183	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Aliskiren 150 to 300 mg QD (n=125) vs lisinopril 20 to 40 mg QD (n=58) HCTZ may be added to aliskiren 300 mg or lisinopril 40 mg if additional blood pressure control was required. The study did not specifically analyze the effects of HCTZ on either treatment regimen.	PG, RCT Men and women with uncomplicated severe hypertension (mean sitting DBP 105-119 mm Hg)	8 weeks	Safety Secondary: Change in mean sitting DBP and SBP, percentage of responders	Both active treatments were well tolerated with an incidence of adverse events of 32.8% for aliskiren and 29.3% for lisinopril. The proportion of patients discontinuing treatment due to adverse events was 3.2% for aliskiren and 3.4% for lisinopril. The most frequently reported adverse events in both groups were headache, nasopharyngitis and dizziness (no *P* values were reported for this endpoint). Secondary: Aliskiren showed similar reductions from baseline to lisinopril in mean sitting DBP (–18.5 vs –20.1 mm Hg) and SBP (–20.0 and –22.3 mm Hg; no *P* values were reported). Responder rates were 81.5% with aliskiren and 87.9% with lisinopril. Approximately half of the patients required the addition of HCTZ to achieve blood pressure control (53.6% for aliskiren and 44.8% for lisinopril; no *P* values were reported).
Anderson et al[19] Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD The addition of HCTZ was permitted at week 12 in patients not achieving adequate blood pressure control (<140/90 mm Hg). The study did not specifically analyze the effects of HCTZ on either treatment regimen.	AC, DB, MC, PC, RCT Men and women ≥18 years with essential hypertension (mean sitting DBP 90-109 mm Hg)	N=842 26 weeks (active treatment)	Primary: Change in mean sitting DBP at week 26 Secondary: Change in mean sitting SBP at week 26, change in mean sitting SBP and DBP at week 6 and 12 (comparing aliskiren and ramipril monotherapy), proportion achieving blood pressure control (<140/90 mm Hg), proportion	Primary: Reductions in mean sitting DBP at week 26 were significantly greater with aliskiren-based therapies (–13.2 mm Hg) than with ramipril-based therapies (–12.0 mm Hg; *P*=0.0250). Secondary: Reductions in mean sitting SBP at week 26 were significantly greater with aliskiren-based therapies (–17.9 mm Hg) than with ramipril-based therapies (–15.2 mm Hg; *P*=0.0036). Mean changes in sitting SBP were significantly greater with aliskiren (–12.9 and –14.0 mm Hg, respectively) than ramipril (–10.5 and –11.3, respectively) at weeks 6 and 12 (*P*=0.0041 and *P*=0.0027, respectively). Mean changes in sitting DBP were not significantly greater with aliskiren (–10.5 and –11.3 mm Hg, respectively) than ramipril (–9.5 and –9.7, respectively) at week 6 but were significantly greater at week 12 (*P*=0.0689 and *P*=0.0056, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			achieving SBP control (<140 mm Hg), safety	The proportion of patients achieving overall blood pressure control <140/90 mm Hg was significantly higher with aliskiren-based therapy (61.4%) than with ramipril-based therapy (53.1%; *P*=0.0205) at week 26. Also, the proportion of patients achieving SBP control <140 mm Hg was significantly higher with aliskiren-based therapy (72.5%) than with ramipril-based therapy (64.1%; *P*=0.0075) at week 26. The majority of adverse events reported during the active treatment period were mild or moderate in intensity and transient. Most events occurred at a similar incidence in the 2 groups with the exception of cough which was considered treatment-related in 5.5% of patients receiving ramipril versus 2.1% of patients receiving aliskiren (no *P* values reported).
Obrien et al[20] Aliskiren 150 mg QD for 3 weeks, if ABPM remained ≥135/85 mm Hg, HCTZ 25 mg QD was added for an additional 3 weeks (n=23 with 17 patients receiving HCTZ) vs irbesartan 150 mg QD for 3 weeks, then aliskiren 75 mg QD was added for 3 weeks, then aliskiren 150 mg QD was added for 3 weeks (n=23) vs ramipril 5 mg QD for 3	3 OL studies Men and women 18-80 years with ambulatory SBP ≥140 and ≤180 mm Hg without treatment	N=67 6-9 weeks	Primary: Change in daytime systolic ABPM with combination therapy compared with monotherapy Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart rates, plasma renin activity	Primary: Aliskiren coadministered with HCTZ (*P*=0.0007) or ramipril (*P*=0.03) led to significantly greater reductions in daytime systolic ABPM compared to monotherapy. There was a trend for a reduction in daytime systolic ABPM with the addition of aliskiren to irbesartan; however, this trend was not statistically significant (*P* value not reported). Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (*P*=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (*P*=0.06 and *P*=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen. Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (all *P*<0.05). No changes in heart rate were observed with either irbesartan regimen. Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (*P*<0.05) but not aliskiren 75 mg (*P* value not reported) to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and diastolic ABPM (all *P*<0.05). No changes in heart

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, then aliskiren 75 mg QD was added for 3 weeks, then aliskiren 150 mg QD was added for 3 weeks (n=21)				rate were observed with either ramipril regimen. Aliskiren alone significantly inhibited plasma renin activity by 65% (*P*<0.0001), while ramipril and irbesartan monotherapy increased renin activity by 90% and 175%, respectively. When aliskiren was coadministered with HCTZ, ramipril or irbesartan, plasma renin activity remained similar to baseline levels or decreased.
Jordan et al[21] Aliskiren 150 mg QD vs amlodipine 5 mg QD vs irbesartan 150 mg QD vs placebo After 4 weeks, doses of aliskiren, irbesartan and amlodipine were doubled and treatment was continued for an additional 8 weeks. All patients continued to received HCTZ 25 mg QD.	DB, DD, MC, PG, RCT Obese men and women (BMI ≥30 kg/m^2) ≥18 years with essential hypertension (mean sitting DBP 95-109 mm Hg and SBP <180 mm Hg) who had not responded to 4 weeks of treatment with HCTZ 25 mg	N=489 16 weeks (4 weeks of HCTZ monotherapy and 12 weeks of combination therapy)	Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at 8 weeks Secondary: Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of responders (mean sitting DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), proportion of patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), plasma renin activity, safety and tolerability	Primary: Aliskiren 300 mg added to HCTZ 25 mg significantly reduced mean sitting DBP compared with HCTZ alone at week 8 (mean difference, –4.0; *P*<0.0001). Secondary: Aliskiren 300 mg added to HCTZ caused numerically larger reductions in mean sitting DBP and SBP compared with amlodipine 10 mg plus HCTZ and irbesartan 300 mg plus HCTZ at week 8, but there were no statistically significant differences between treatment groups (*P*>0.05). Responder rates were significantly higher with aliskiren plus HCTZ than HCTZ alone at week 8 (*P*=0.0193) and week 12 (*P*=0.004) but comparable to responder rates observed with amlodipine plus HCTZ (*P*>0.05) and irbesartan plus HCTZ (*P*>0.05). The proportion of patients achieving blood pressure control was significantly higher with aliskiren plus HCTZ than HCTZ alone at week 8 (*P*=0.0005) and week 12 (*P*=0.0001) but not statistically different than amlodipine plus HCTZ (*P*>0.05) and irbesartan plus HCTZ (*P*>0.05). Plasma renin activity significantly increased (*P*<0.05) during 4 weeks of HCTZ monotherapy. Combination with aliskiren neutralized this increase and led to an overall significant reduction in plasma renin activity compared with pretreatment baseline (*P*<0.05) whereas amlodipine and irbesartan led to further significant increases (*P*<0.05). All of the study treatments were generally well tolerated. Amlodipine plus HCTZ (45.2%) was associated with a higher incidence of adverse events

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				than the other treatment groups (36.1% to 39.3%; no *P* values reported), largely due to a higher rate of peripheral edema (11.1% vs 0.8% to 1.6%; no *P* values reported).

Drug regimen abbreviations: HCTZ=hydrochlorothiazide, QD=once daily
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, DBP=diastolic blood pressure, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Combination Renin Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
aliskiren and hydrochlorothiazide	tablet	Tekturna HCT®	$$$	N/A

No generic products are available in this class.
N/A=not available.

X. Conclusions

Aliskiren plus hydrochlorothiazide (Tekturna HCT®) is the only combination renin inhibitor marketed in the United States and it is Food and Drug Administration approved for the treatment of hypertension.[2] The fixed-dose combination product is not recommended for initial therapy and it is not available generically.

Aliskiren has been evaluated in combination with hydrochlorothiazide in a few clinical trials but none of the published trials have specifically evaluated the fixed-dose formulations.[17-21] In addition, there are currently no published studies that have compared the administration of the fixed-dose combination product to administration of the individual components or to any other antihypertensive regimens. There are no long-term trials evaluating the safety and efficacy of aliskiren or determining whether aliskiren improves clinical outcomes. Like other drugs that act directly on the renin-angiotensin-aldosterone system (RAAS), aliskiren carries a black box warning against use during pregnancy.[2] To date the role of renin inhibitors, either the single entity or fixed-dose combination products, has not been addressed by the national and international consensus guidelines for the management of hypertension.

At this time, there is insufficient data to conclude that the combination renin inhibitors offer significant clinical advantage over other alternatives in general use. Therefore all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over the other alternatives in general use.

XI. Recommendations

No brand combination renin inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Loop Diuretics
AHFS Class 402808
September 10, 2008

I. Overview

Diuretics have been widely used for many years in the treatment of hypertension, heart failure, and various edematous conditions.[1,2] They diminish sodium chloride reabsorption at different sites along the nephron, and therefore increase urinary sodium chloride and water loss.[3] Diuretics are considered to be first-line treatment for patients with chronic heart failure, because they provide symptomatic relief, improve cardiac function and exercise tolerance, increase sodium urinary excretion, and decrease the physical signs of fluid retention.[4] Thiazide-type diuretics are considered initial therapy for hypertension in most patients who do not have other significant comorbid conditions.[5] Diuretic classes differ in their specific mechanisms of action, sites of action, and chemical structures. The American Hospital Formulary Service (AHFS) places the diuretic agents into 6 classes, 4 of which will be covered in this series of reviews: Loop Diuretics, Potassium-sparing Diuretics, Thiazide Diuretics, and Thiazide-like Diuretics.[6] The classes of Osmotic Diuretics and Miscellaneous Diuretics are administered primarily on an inpatient basis in institutions, and will not be included.

Loop diuretics inhibit the reabsorption of sodium in the ascending limb of the loop of Henle. Furosemide and ethacrynic acid additionally inhibit the reabsorption of sodium in the proximal and distal tubules.[7] Bumetanide inhibits reabsorption in the proximal tubule, but not within the distal tubule.[7] When loop diuretics are given at their maximum dosages, they can lead to the excretion of up to 20%-25% of the filtered sodium.[3] They are considered to be the most potent diuretics, and as renal function declines to a glomerular filtration rate of less than 30 mL/minute, a loop diuretic should be considered rather than a thiazide diuretic.[1] Loop diuretics provide the most diuresis, but they do not possess the added property of arterial vasodilation as seen with the thiazide diuretics. Some studies have suggested that hydrochlorothiazide (a thiazide diuretic) is more effective in lowering blood pressure than loop diuretics.[8]

The loop diuretics that are included in this review are listed in Table 1. As noted in the table, there are several generic formulations of the loop diuretics. This review encompasses all dosage forms and strengths.

Table 1. Loop Diuretics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
bumetanide	injection, tablet	Bumex®*	bumetanide
ethacrynate sodium	injection	Edecrin Sodium®	none
ethacrynic acid	tablet	Edecrin®	Edecrin®
furosemide	injection, oral solution, tablet	Lasix®*	Lasix®, furosemide
torsemide	injection, tablet	Demedex®*	torsemide

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the loop diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of hypertension and heart failure, please refer to the Appendix

Table 2. Treatment Guidelines Using the Loop Diuretics

Clinical Guideline	Recommendation
American College of Cardiology (ACC)/American Heart	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary

Clinical Guideline	Recommendation
Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[17]	guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. <u>Patients With Current or Prior Symptoms of Heart Failure (Stage C)</u> • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. <u>Patients With Heart Failure and Normal Left Ventricular Ejection Fraction</u> • Diuretics are recommended to control pulmonary congestion and peripheral edema. <u>Patients With Refractory End-Stage Heart Failure (Stage D)</u> • Treatment of fluid retention is important.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[18]	<u>Patients With Left Ventricular Systolic Dysfunction</u> • An aldosterone antagonist may be added to the standard medication regimen (including diuretics) in patients who are in New York Heart Association (NYHA) functional class IV or those in class III previously in class IV (left ventricular ejection fraction ≤35%) from left ventricular systolic dysfunction. • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics are typically preferred. • Torsemide may be considered in patients in whom erratic diuretic effect or absorption is present. • Metolazone or chlorothiazide may be given to patients with persistent fluid retention despite high dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion. <u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u> • Diuretics are recommended in patients with evidence of fluid overload. <u>Patients With Acute Decompensated Heart Failure</u> • Intravenous vasodilators, diuretics, and inotropes have all been used to treat patients with acute decompensated heart failure. <u>Managing Patients With Heart Failure and Hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or a calcium channel blocking agent (CCB). • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)**[19]	• ACE inhibitors are recommended in patients with left ventricular ejection fraction 40%-45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention. • Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated. • Aldosterone antagonists are recommended in addition to ACE inhibitors, β-blockers, and diuretics in patients who have advanced heart failure (NYHA class III-IV) with

Clinical Guideline	Recommendation
	systolic dysfunction, and in patients who are unable to tolerate therapy with ACE inhibitors. • A combination of digoxin and a β-blocker seems to be more efficacious to either agent alone in patients with atrial fibrillation. Digoxin may reduce hospitalizations in patients with heart failure caused by left ventricular systolic dysfunction and sinus rhythm who are already treated with ACE inhibitors, β-blockers, diuretics, and spironolactone (in severe heart failure).
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[5]	• High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[9]	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[10]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics).
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[11]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients. • Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension	• If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added.

Clinical Guideline	Recommendation
Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[12]	• If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[13]	• No specific recommendation is made concerning loop diuretics.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[14]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[15]	• Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[16]	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence.

III. Indications

Food and Drug Administration (FDA)-approved indications for the loop diuretics 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 Loop Diuretics[2,6-7,20-26]

Indication	Bumetanide	Ethacrynic Acid and Ethacrynate Sodium	Furosemide	Torsemide
Treatment of hypertension either alone or in combination with other antihypertensive drugs			✔	✔
Adult treatment of edema associated with congestive heart failure, hepatic disease or renal disease including nephrotic syndrome	✔	✔	✔	✔
Pediatric treatment of edema associated with congestive heart failure, hepatic disease and renal disease including nephritic syndrome		✔ *	✔	
Short-term management of ascites due to malignancy, idiopathic edema, and lymphedema		✔		
Short-term management of hospitalized pediatric patients, other than infants, with congenital heart disease or nephrotic syndrome		✔		
Adjunctive therapy in acute pulmonary edema			✔ †	
When a rapid onset of diuresis is desired (eg, in acute pulmonary edema), or when gastrointestinal absorption is impaired or oral medication is not practical)		✔ †	✔ †	✔ †

*Safety and effectiveness of intravenous use in pediatric patients have not been established. Safety and effectiveness of oral and parenteral use in infants have not been established.
†Intravenous formulation only.

IV. Pharmacokinetics

The pharmacokinetic parameters for the loop diuretics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Loop Diuretics[2,,6,7,20-26]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination (%)	Half-Life (hours)
Bumetanide	80-95	95	Hepatic	Unknown	50-81	Feces (10-50)	1-2
Ethacrynate sodium	100	90	Hepatic	None	66	Not reported	1-4
Ethacrynic acid	100	90	Hepatic	None	66	Not reported	1-4
Furosemide	43-70	91-99	Hepatic (10%)	Furosemide glucuronide	60-90	Biliary (6-9), feces (7-9)	0.5-2 increases in heart and renal failure
Torsemide	80-90	99	Hepatic	M1 and M3	60-82	Not reported	3.5-6

V. Drug Interactions

Significant drug interactions with the loop diuretics are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Loop Diuretics[2]

Drug(s)	Significance Level	Interaction	Mechanism
Loop diuretics (all)	1	Aminoglycosides (amikacin, gentamicin, kanamycin, netilmicin, streptomycin, tobramycin)	Auditory toxicity may be increased by possible synergistic activity. The mechanism is unknown.
Loop diuretics (bumetanide, ethacrynic acid, furosemide. torsemide)	1	Cisapride	Risk of life threatening cardiac arrhythmias including torsades de pointes may be increased due to the rapid electrolyte loss from loop diuretics in acute settings.
Loop diuretics (bumetanide, ethacrynic acid, furosemide)	1	Digitalis glycosides (digitalis, digitoxin, digoxin)	Diuretic-induced electrolyte disturbances may predispose digitalis induced cardiac arrhythmias.
Loop diuretics (all)	2	Cisplatin	Additive ototoxicity may occur when used in combination. The mechanism is not known.
Loop diuretics (all)	2	Lithium	Increased plasma lithium concentrations increase risk of toxicity. The mechanism is unknown.
Loop diuretics (all)	2	Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate carefully in small or intermittent doses.
Furosemide	2	Bile acid sequestrants (cholestyramine, colestipol)	Concurrent administration of furosemide and bile acid sequestrants results in a decrease of furosemide absorption; thereby a decrease in pharmacologic effects may occur.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Events

The most common adverse reactions reported with the loop diuretics are noted in Table 6. Additionally, details of the black box warning regarding the risk of profound diuresis with ethacrynic acid can be found in Table 7.

Table 6. Adverse Drug Events (%) Associated with the Loop Diuretics[2,6-7,20-26]

Adverse Event	Bumetanide	Ethacrynate sodium	Ethacrynic acid	Furosemide	Torsemide
Cardiovascular					
Atrial Fibrillation	-	-	-	-	✔
Chest pain	0.1	-	-	-	1.2
Edema	-	-	-	-	1.1
Electrocardiogram changes	0.4	-	-	-	2.0
Hypotension	0.8	-	-	✔	✔
Hypovolemia	-	-	✔	-	✔
Myalgia	-	-	-	-	1.6
Orthostatic hypotension	-	-	-	✔	✔
Shunt thrombosis	-	-	-	-	✔
Syncope	-	-	-	-	✔
Ventricular tachycardia	-	-	-	-	✔
Central Nervous System					
Apprehension	-	-	✔	-	-

Adverse Event	Bumetanide	Ethacrynate sodium	Ethacrynic acid	Furosemide	Torsemide
Asterixis	0.1	-	-	-	-
Asthenia	-	-	-	✔	2.0
Confusion	-	-	✔	-	-
Dizziness	1.1	-	-	✔	3.2
Fatigue	0.1	-	✔	-	✔
Headache	0.6	-	✔	✔	7.3
Insomnia	-	-	-	-	1.2
Nervousness	-	-	-	-	1.1
Paresthesia	-	-	-	✔	-
Vertigo	0.1	-	✔	✔	-
Xanthopsia	-	-	-	✔	-
Dermatologic					
Erythema multiforme	-	-	-	✔	-
Exfoliative dermatitis	-	-	-	✔	-
Hives	0.2	-	-	-	-
Itching	0.1	-	-	-	-
Pruritus	0.4	-	-	✔	✔
Rash	0.2	✔	✔	✔	✔
Photosensitivity	-	-	-	✔	-
Purpura	-	-	-	✔	-
Scaling eczema	-	-	-	✔	-
Stevens-Johnson Syndrome	-	-	-	✔	-
Urticaria	-	-	-	✔	-
Hypersensitivity					
Angioedema	-	-	-	-	✔
Interstitial nephritis	-	-	-	✔	-
Necrotizing angitis	-	-	-	✔	-
Systemic vasculitis	-	-	-	✔	-
Gastrointestinal					
Abdominal discomfort/pain	0.2	✔	✔	-	-
Anorexia	-	✔	✔	✔	-
Constipation	-	-	-	✔	1.8
Diarrhea	0.1	✔	✔	✔	2.0
Dyspepsia	0.1	✔	-	✔	1.6
Dysphagia	-	-	✔	-	✔
Gastrointestinal bleed	-	✔	✔	-	✔
Loss of appetite	-	-	-	✔	-
Malaise	-	✔	✔	-	-
Nausea	0.6	✔	✔	✔	2.0
Pancreatitis	-	✔	✔	✔	-
Polydipsia	-	-	-	-	✔
Vomiting	0.2	✔	✔	✔	✔
Hematologic					
Agranulocytosis	-	✔	✔	✔	-
Anemia	-	-	-	✔	-
Aplastic anemia	-	-	-	✔	-
Deviations in differential counts	0.1	-	-	-	-
Deviations in hematocrit	0.6	-	-	-	-
Deviations in hemoglobin	0.8	-	-	-	-
Deviations in prothrombin time	0.8	-	-	-	-
Deviations in white blood cell count	0.3	-	-	-	-
Hemolytic anemia	-	-	-	✔	-

Adverse Event	Bumetanide	Ethacrynate sodium	Ethacrynic acid	Furosemide	Torsemide
Henoch-Schonlein purpura	-	-	✔	-	-
Leukopenia	-	-	-	✔	-
Neutropenia	-	✔	✔	-	-
Thrombocytopenia	0.2	✔	✔	✔	-
Hepatic					
Abnormal liver enzymes	✔	✔	✔	-	-
Change in alanine aminotransferase	0.5	-	-	-	-
Change in aspartate aminotransferase	0.6	-	-	-	-
Encephalopathy	0.6	-	-	-	-
Jaundice	-	✔	✔	✔	-
Lab Test Abnormalities					
Azotemia	10.6	-	-	-	-
Hyperglycemia	6.6	✔	✔	✔	✔
Hyperuricemia	18.4	✔	✔	✔	✔
Hypochloremia	14.9	-	-	-	-
Hypokalemia	14.7	-	✔	✔	✔
Hyponatremia	9.2	-	-	-	-
Increased serum creatinine	7.4	-	-	-	-
Variations in bicarbonate	3.1	-	-	-	-
Variations in calcium	2.4	-	-	-	-
Variation in CO_2 content	4.3	-	-	-	-
Variations in phosphorus	4.5	-	-	-	-
Metabolic					
Acute gout	-	✔	✔	-	✔
Dehydration	0.1	-	-	-	-
Electrolyte imbalance	-	-	-	✔	✔
Hyperlipidemia	✔	-	✔	✔	✔
Hypocalcemia	✔	✔	✔	✔	✔
Hypoglycemia	-	-	✔	-	-
Hypomagnesemia	✔	-	✔	✔	✔
Miscellaneous					
Arthralgia	-	-	-	-	1.8
Changes in alkaline phosphatase	0.4	-	-	-	-
Changes in cholesterol	0.4	-	-	-	-
Changes in serum proteins	0.7	-	-	-	-
Changes in total serum bilirubin	0.8	-	-	-	-
Chills	-	✔	✔	-	-
Difficulty maintaining an erection	0.1	-	-	-	-
Dry mouth	0.1	-	-	-	-
Fever	-	✔	✔	✔	-
Hematuria	-	-	✔	-	-
Nipple tenderness	0.1	-	-	-	-
Premature ejaculation	0.1	-	-	-	-
Restlessness	-	-	-	✔	-
Sore Throat	-	-	-	-	1.6
Sweating	0.1	-	-	-	-
Thrombophlebitis	-	-	-	✔	-
Weakness	0.2	-	-	✔	✔
Musculoskeletal					
Arthritic pain	0.2	-	-	-	✔
Cramps	1.1	-	-	✔	✔
Musculoskeletal pain	0.2	-	-	-	-

Adverse Event	Bumetanide	Ethacrynate sodium	Ethacrynic acid	Furosemide	Torsemide
Spasticity	-	-	-	✔	-
Renal					
Changes in creatinine clearance	0.3	-	-	-	-
Glycosuria	0.7	-	-	✔	-
Polyuria	-	-	-	-	6.7
Proteinuria	0.3	-	-	-	-
Renal Failure	0.1	-	-	-	-
Respiratory					
Cough	-	-	-	-	2.0
Hyperventilation	0.1	-	-	-	-
Rhinitis	-	-	-	-	2.8
Special Senses					
Blurred vision	-	✔	✔	✔	-
Deafness	-	✔	✔	-	-
Ear discomfort	0.1	-	-	-	-
Fullness of ears	-	-	✔	-	-
Impaired hearing	0.5	-	✔	✔	-
Ototoxicity	-	✔	✔	-	✔
Tinnitus	-	✔	✔	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 7. Black Box Warning for Bumetanide, Ethacrynate sodium, Ethacrynic acid, and Furosemide (oral)[2]

Profound Diuresis
These agents are potent diuretics which, if given in excessive amounts, may lead to profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule must be adjusted to the individual patient's needs (see Administration and Dosage).

VII. Dosing and Administration

The usual dosing regimens for the loop diuretics are summarized in Table 8.

Table 8. Usual Dosing for the Loop Diuretics[2,6-7,20-26]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Bumetanide	Edema: Intramuscular/intravascular: 0.5 to 1.0 mg over 1 minute; maximum, 10 mg/day Tablet: 0.5 to 2.0 mg/day; maximum, 10 mg/day	Safety and efficacy in children have not been established.	Ampule, disposable syringe, vial: 0.25 mg/mL Tablet: 0.5 mg 1 mg 2 mg
Ethacrynate sodium	Edema: Intravascular: 0.5 to 1.0 mg/kg; maximum dose, 100 mg	Edema: Intravascular: 1 mg/kg over 20 to 30 minutes for one dose (not Food and Drug Administration (FDA) approved in infants)	Powder for injection: 50 mg/vial
Ethacrynic acid	Edema: Tablet: 50 to 400 mg/day	Edema: Tablet: 25 mg/kg; maximum dose, 3 mg/kg/day (not FDA approved in infants)	Tablet: 25 mg
Furosemide	Edema: Intramuscular: 20 to 40 mg once or	Edema: Intramuscular:	Ampule, disposable syringe and vial:

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	twice daily, may repeat in 2 hours or increased by 20 mg until desired response Intravascular: 20 to 40 mg over 1 to 2 minutes Tablet: 20 to 80 mg/day, may repeat in 6 to 8 hours; maximum, 600 mg/day <u>Hypertension:</u> Tablet: 80 mg/day <u>Refractory edema/ heart failure:</u> Intravascular: 250 to 4,000 mg/day Tablet: 250 to 4,000 mg/day	Neonates <29 weeks gestation, 1 mg/kg/dose every 24 hours Neonates >29 weeks gestation, 1 mg/kg/dose every 12 to 24 hours Neonates, 1 to 3 mg/kg every 8 hours Infants and children, initial 1 mg/kg/dose, may increase by 0.25 to 0.5 mg/kg/dose with succeeding doses at intervals of 4 to 12 hours; maximum of 10 mg/kg/24 hours Intravascular: Neonates <29 weeks gestation, 1 mg/kg/dose every 24 hours Neonates >29 weeks gestation, 1 mg/kg/dose every 12 to 24 hours Neonates, 1-3 mg/kg every 8 hours, over 3 minutes Infants and children, initial 1 mg/kg/dose, may increase by 0.25 to 0.5 mg/kg/dose with succeeding doses at intervals of 4 to 12 hours; maximum of 10 mg/kg/24 hours Oral: Neonates <29 weeks gestation, 1 to 2 mg/kg/dose every 24 hours; maximum, 6 mg/kg/dose Neonates >29 weeks gestation, 1 to 2 mg/kg/dose every 12 to 24 hours; maximum 6 mg/kg/dose Neonates, 1 to 3 mg every 8 hours Infants and children, initial, 2 mg/kg/dose; may increase by 1 to 2 mg/kg/dose no sooner than 6 to 8 hours following previous dose; maximum, 6 mg/kg/dose	10 mg/mL Oral solution: 10 mg/1 mL 40 mg/5 mL Tablet: 20 mg 40 mg 80 mg
Torsemide	<u>Edema:</u> Intravascular: 5 to 40 mg/day; maximum of 200 mg/day Tablet: 5 to 40 mg/day; maximum of 200 mg/day <u>Hypertension:</u> Tablet: 5 to 10 mg/day	Safety and efficacy in children have not been established.	Ampule: 10 mg/mL Tablet: 5 mg 10 mg 20 mg 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the loop diuretics are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Loop Diuretics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Heart Failure/Edema				
Faris et al[4] One diuretic (loop diuretics [furosemide, bumetanide], thiazide diuretics [chlorothiazide], or potassium-sparing diuretics [amiloride, triamterene]) vs placebo or with open control or one diuretic (loop diuretics [furosemide, bumetanide], thiazide diuretics [chlorothiazide], or potassium-sparing diuretics [amiloride, triamterene]) vs another active agent (eg, angiotensin converting enzyme inhibitors, digoxin)	MA 14 double-blinded, randomized control trials of diuretic therapy comparing loop, thiazide, or potassium-sparing diuretics with placebo or with open control; or one diuretic with another active agent in adult patients with chronic heart failure	N=525 2 to 52 weeks	Primary: Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Primary: Mortality was reported in 3 of the 7 placebo-controlled trials, and this analysis showed that mortality was lower for patients treated with diuretics than with placebo (3/111[2.7%] vs 12/110 [10.9%], respectively; OR 0.24; 95% CI, 0.07 to 0.83; *P*=0.02). These results showed that patients treated with diuretics had an absolute risk reduction of 8% when compared to placebo and a number needed to treat of 12.5. Secondary: An analysis of pooled data from 2 trials showed lower admission rates for worsening heart failure in patients taking diuretics than in patients taking placebo (OR 0.07; 95% CI, 0.01 to 0.52; *P*=0.01). Diuretics were found to improve exercise capacity, with a difference in means of 0.74 (95% CI, 0.37 to 1.11; *P*<0.0001) and of 0.67 (95% CI, 0.02 to 1.31; *P*=0.04.), respectively. The combined results of these 4 trials indicated that diuretics improved exercise capacity in participants with chronic heart failure with a difference in means of 0.72 (95% CI, 0.40 to 1.04; *P*<0.0001).
Eshaghian et al[27]	Cohort study, SC	N=1,354	Primary: All-cause mortality	Primary: There were 269 deaths during the 2-year follow-up, with 182 deaths by

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Furosemide 0 to 40 mg daily (group 1) vs furosemide 41 to 80 mg daily (group 2) vs furosemide 81 to 160 mg daily (group 3) vs furosemide >160 mg daily (group 4)	Men and women with advanced systolic heart failure referred to a single university medical center for heart failure management and/or transplant evaluation from 1985 to 2004	2 years	Secondary: Composite endpoint of death or urgent transplant	year 1 and 87 deaths during year 2. Of the 269 deaths, 91 deaths were due to progressive heart failure, 72 deaths were sudden, 8 deaths were secondary to myocardial infarction and 101 were unknown. Survival estimates at 1 year were 91%, 88%, 80%, and 69% for groups 1, 2, 3, and 4, respectively (*P*<0.0001). Survival estimates at 2 years were 83%, 81%, 68% and 53%, respectively (*P*<0.0001). Secondary: There were a total of 431 patients who received heart transplants by the end of the 2-year follow-up: 223 urgent and 208 elective. The hazard ratios for death from any cause, death and urgent transplantation, death from progressive heart failure, and sudden death for group 4 compared with group 1 were similar (*P* value not reported). On univariate analysis, compared with group 1, increasing loop diuretic dose were associated with a progressive increase in mortality (group 2: HR, 1.2; 95% CI, 0.8 to 1.7, group 3: HR, 2.1; 95% CI, 1.5 to 2.9, and group 4: HR, 3.4; 95% CI, 2.4 to 4.7).
Patterson et al[28] Torsemide 5 mg QD vs torsemide 10 mg QD vs torsemide 20 mg QD vs placebo QD	DB, PC, MC, PG Men and women diagnosed with NYHA class II or III congestive heart failure and edema	N=66 7 days	Primary: Change in body weight from baseline Secondary: Change in urinary sodium, potassium, chloride excretion and urine volume after the first dose of drug	Primary: Patients receiving torsemide 10 and 20 mg had a significant decrease in weight (-1.62 and -1.30 kg, respectively) as compared to placebo (*P* value not reported). Torsemide 5 mg did not demonstrated a significant reduction in body weight compared to placebo (-0.60 kg; *P* value not reported). Secondary: Severity of edema decreased as the dose of torsemide increased. The adverse events did not increase with higher doses of torsemide (*P* value not reported).
Hutcheon et al[29] Bumetanide 1 to 2 mg/day	DB, PG Patients with severe edema associated	N=20 3 days	Primary: Edema, symptoms of heart failure, safety and	Primary: Each agent was effective in decreasing the edema and relieving the symptoms of heart failure (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs furosemide 80 mg/day	with congestive heart failure		tolerability Secondary: Not reported	Side effects were not severe and were similar in both treatment groups. Muscle cramps and abdominal pain were deemed not severe. Electrolyte shifts indicative of hypochloremic alkalosis and hyponatremia were seen in two patients in the bumetanide group. Secondary: Not reported
Konecke et al[30] Bumetanide vs furosemide No dose and frequency reported for both.	OL, PG, RCT Men and women with clinically detectable edema and signs and symptoms of congestive heart failure (eg, rales, gallop rhythm, orthopnea, dyspnea, engorged neck veins, paroxysmal nocturnal dyspnea, congested liver, etc.)	N=42 6 months	Primary: Changes in weight, blood pressure, pulse, signs and symptoms of congested heart failure, electrolytes and functional capacity, safety and tolerability Secondary: Not reported	Primary: There were no statistical differences in changes in body weight, blood pressure, edema, abdominal girth, and hepatomegaly and other signs and symptoms of congestive heart failure in patients receiving bumetanide vs furosemide (*P* value not reported). There were variable minor changes in serum sodium, potassium, chloride, and uric acid in both groups throughout the treatment (*P* value not reported). Changes remained within normal limits and reached significance for chloride at weeks 8 and 16 in the bumetanide group. Functional capacity improved slightly or remained unchanged throughout treatment in both treatment groups (*P* value not reported). There were no major side effects that were medication related in both treatment groups. Secondary: Not reported
Nicholson et al[31] Bumetanide 1 mg/day alternating with 3 mg/day for 3 months vs frusemide* 40 mg/day alternating with 160 mg/day for 3 months	RCT, XO Patients with cirrhosis and fluid overload	N=10 6 months	Primary: Ascites and edema Secondary: Adverse events	Primary: Bumetanide and frusemide were both effective in controlling ascites and edema, with 9 out of 10 patients showing a satisfactory response (*P* value not reported). Secondary: Side effects were reported in 6 patients. The most common side effects were urinary frequency and nocturia, which occurred in 4 patients taking bumetanide and 1 patient taking frusemide. There was 1 patient on bumetanide and 1 patient on frusemide who developed symptoms of postural hypotension.
Austin et al[32]	OS	N=27	Primary: Hemodynamic	Primary: The hemodynamic response with each medication was similar. When

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ethacrynic acid 25 to 50 mg infused through a pulmonary artery catheter vs furosemide 40 to 60 mg infused through a pulmonary artery catheter	Men and women who underwent diagnostic right and transeptal left heart catheterization with chronic postcapillary pulmonary hypertension with heart failure NYHA Class II-IV	1 hour	response (in the control state and at 20, 40, and 60 minutes after diuretic administration) including cardiac index, pulmonary artery, left atrial and systemic artery mean pressures, plasma volume, PBV and PEV Secondary: Not reported	compared to control state, the reductions in pulmonary artery mean pressure at 20, 40, and 60 minutes after diuretic infusion with either ethacrynic acid or furosemide were significant (*P*<0.001). The average left atrial mean pressure also decreased from 22 mm Hg during the control period to 18 mm Hg at 20 minutes and to 15 mm Hg at 60 minutes post diuretic infusion (ethacrynic acid or furosemide; *P*<0.001). The mean cardiac index decreased significantly at 20, 40, and 60 minutes compared to the control state after diuretic infusion with either ethacrynic acid or furosemide (*P*<0.001). There was a significant decrease in plasma volume at 60 minutes post drug infusions (ethacrynic acid or furosemide; *P*<0.001). In contrast, there was no significant change in PBV, PEV, PEV/PBV, and systemic arterial pressure throughout the study period with ethacrynic acid or furosemide (*P* value not reported). Secondary: Not reported
Muller K et al[33] Furosemide vs torasemide[†]	Prospective, R Patients with congestive heart failure (NYHA II-IV) on an angiotensin converting enzyme inhibitor in a primary care setting	N=237 9 months	Primary: Clinical improvement in heart failure, quality of life, hospitalizations and safety and tolerability Secondary: Not reported	Primary: Clinical improvement in chronic heart failure was seen in both groups but the trend to improve by at least one NYHA class was significant with torsemide (*P*=0.014) but not in furosemide-treated patients (*P* value not reported). There were no differences in adverse reactions and hospitalizations due to congestive heart failure (*P* value not reported). Secondary: Not reported.
Kasama et al[34] Furosemide 20 to 40 mg/day vs	RCT Patients with non-ischemic congestive heart failure (left ventricular ejection	N=40 6 months	Primary: Effect on cardiac sympathetic nerve activity (delayed heart to mediastinum count	Primary: In the furosemide group at the end of treatment, mean heart to mediastinum count ratio increased from 1.68±0.18 to 1.71±0.19 (*P*=NS), mean total defect score decreased from 42±11 to 40±12 (*P*=NS), and mean washout rate decreased from 50±8% to 47±12% (*P*=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
torasemide† 4 to 8 mg/day	fraction <45%) also being treated with an angiotensin converting enzyme inhibitor		ratio, delayed total defect score, washout rate) Secondary: Effect on left ventricular remodeling (left ventricular end diastolic volume, left ventricular end systolic volume)	In the torasemide group at the end of treatment, mean heart to mediastinum count ratio increased from 1.61±0.19 to 1.77±0.24 (*P*<0.001), mean total defect score decreased from 44±8 to 36±8 (*P*<0.001), and mean washout rate decreased from 52±12% to 41±14% (*P*=0.001). Secondary: In the furosemide group left ventricular end diastolic volume decreased from 174±24 mL to 165±34 mL (*P*=NS), left ventricular end systolic volume decreased from 120±15 mL to 109±33 mL (*P*=NS), and left ventricular ejection fraction increased from 31±7% to 32±7% (*P*=NS). In the torasemide group left ventricular end diastolic volume decreased from 173±22 mL to 147±30 mL (*P*<0.01), left ventricular end systolic volume decreased from 117±19 mL to 95±25 mL (*P*<0.001), and left ventricular ejection fraction increased from 31±7% to 34±7% (*P*=NS).
Senzaki et al[35] Torasemide† (de novo group) vs torasemide† (replacement group) was converted from furosemide dosage using 0.2 mg torasemide corresponding to 1 mg furosemide	RCT Pediatric patients (age range from 3 weeks to 17 years) with congested heart failure, patients newly diagnosed with congestive heart failure or previously treated with furosemide	N=102 3-4 weeks	Primary: Clinical signs and symptoms of congestive heart failure Secondary: Humoral factors, serum potassium levels, and adverse events	Primary The de novo torasemide group significantly improved the congestive heart failure index from 7.2±1.6 to 5.7±1.4 (*P*<0.05); however the replacement group did not. The replacement group baseline value of the congestive heart failure index was 7.4±2.4 and after treatment the mean value was 6.8±2.3. Secondary: The de novo and replacement groups significantly improved brain natriuretic peptide and aldosterone levels (*P*<0.05); however plasma rennin activity was not significantly decreased among both groups. Serum potassium levels were significantly increased in the replacement group (*P*<0.05) but not in the de novo group. The most commonly reported adverse events of torasemide were those associated with loop diuretics in general.
Hypertension				
De Berrazueta et al[36] Furosemide infused in 3 progressive solutions containing 475, 950, and	RCT Patients with hypertension and healthy controls	N=59 Single dose	Primary: Dilatory effect on arteries and veins Secondary:	Primary: There were no significant changes in arterial dilation. Furosemide increased vasodilatation from 0.56±0.09 to 0.88±0.06 (*P*=0.000) in healthy control subjects and from 0.49±0.10 to 0.75±0.12 (*P*=0.000) in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1,900 nmol/mL for arterial studies and 240, 480, and 960 nmol/mL for venous studies vs torasemide† infused in 3 progressive solutions containing 400, 800, and 1,600 nmol/mL for arterial studies and 200, 400, and 800 nmol/mL for venous studies			Not reported	hypertensive patients. Torasemide increased venodilation from 0.46±0.06 to 0.70±0.11 (*P*=0.007) in control subjects and from 0.48±0.09 to 0.67±0.12 (*P*=0.03) in hypertensive patients. Secondary: Not reported
Von Dossow et al[37] Furosemide 40 mg IV and 80 mg PO 2 hours after extubation on day 1 after surgery vs torasemide† 20 mg IV and 20 mg PO 2 hours after extubation on day 1 after surgery	DB, RCT Patients with secondary pulmonary hypertension scheduled for elective valve replacement and/or coronary artery bypass graft	N=21 Day 1 after surgery	Primary: Cardiac output Secondary: Endothelin-1 and angiotensin-II	Primary: Cardiac output increased significantly (*P*=0.03) in the torasemide group compared to the furosemide group. Secondary: Endothelin-1 and angiotensin-II increased significantly (*P*=0.031) in the furosemide group compared to the torasemide group.
Van der Heijden et al[38] Placebo daily for 5 weeks then bumetanide 1 mg daily for 6 weeks then placebo daily for 6 weeks then furosemide 40 mg daily for 6 weeks vs placebo daily for 6 weeks	DB, PC, XO Patients with a diagnosed of hypertension for at least 6 months	N=27 24 weeks	Primary: Changes in blood pressure, serum lipid levels, lab values and safety and tolerability Secondary: Not reported	Primary: Bumetanide and furosemide reduced SBP by 8.2% (*P*<0.0002) and DBP by 4.5% (*P*<0.002). Overall SBP and DBP measurements were 12 mm Hg and 4 mm Hg lower, respectively, when receiving bumetanide or furosemide vs placebo. Both furosemide and bumetanide increased total cholesterol by 5.0% (*P*<0.002), high-density lipoprotein cholesterol by 1.7% (*P*=NS), low-density lipoprotein cholesterol by 4.8% (*P*<0.01) and triglycerides by 12.4% (*P*<0.01). Serum glucose, magnesium, sodium and potassium levels were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
then furosemide 40 mg daily for 6 weeks then placebo daily for 6 weeks then bumetanide 1 mg daily for 6 weeks				unchanged in both treatment groups; whereas serum creatinine tended to increase (3.2%; *P*=0.09). Side effects were mild in severity with no discontinuation reported. In both bumetanide and furosemide treated patients, four patients reported hypertonic muscles, but was resolved within a couple of days. Secondary: Not reported.
Vasavada et al[39] Phase 1: Inpatient Furosemide 200 mg daily with sodium-free water (10 mL/kg) vs torsemide 100 mg daily with sodium-free water (10 mL/kg) Phase 2: Outpatient furosemide 80 mg daily vs torsemide 40 mg daily	DB, RCT, two-phase, XO Men and women at least 18 years of age, with chronic kidney disease as determined by serum creatinine >1.4 mg/dL, and volume overload defined as hypertension (average of three seated sitting cuff blood pressure >130/80 mm Hg or >125/75 mm Hg if the subject had proteinuria >1 g/day) with or without edema	N=14 3 weeks	Phase 1: Inpatient Primary: Change in 24-hour urinary sodium excretion Secondary: Potassium, calcium, protein excretion, diurnal variation of electrolyte and protein excretion, and glomerular filtration rate Phase 2: Outpatient Primary: 24-hour ambulatory SBP Secondary: Not reported	Phase 1: Inpatient Primary Furosemide and torsemide increased urinary sodium excretion from an average (±SD) 199±49 mEq/day to 357±96 mEq/day and 213±79 mEq/day to 398±142 mEq/day, respectively. These differences between the two diuretics were not statistically significant (*P* value not reported). Secondary: There were no significant differences in excretion rate profiles between torsemide and furosemide (*P*>0.17). Phase 2: Outpatient Primary: Both treatments had similar effects in reducing SBP (*P*=0.43). The SBP was reduced from baseline to post treatment by 9.7±10 mm Hg for torsemide (*P*=0.007) and 9.2±12.6 mmHg for furosemide (*P*=0.021). Secondary: Not reported
Valmin K et al[40] Furosemide 12.5, 25 or 40 mg BID vs	DB, RCT, XO, 5 experimental periods each of 4 weeks Men and women with essential	N=34 20 weeks	Primary: Blood pressure, urinary output, serum electrolytes, safety and tolerability	Primary: When compared to placebo, there was a significant reduction of blood pressure with HCTZ 12.5 mg twice daily and furosemide 12.5 mg twice daily (*P*<0.05). Paired comparison showed that HCTZ 12.5 mg twice daily and furosemide 25 and 40 mg twice daily had a similar hypotensive effect,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HCTZ 12.5 mg BID vs placebo	hypertension		Secondary: Not reported	irrespective of the initial blood pressure (*P*>0.10). When compared to placebo, the urinary output increased significantly with furosemide 12.5, 25, or 40 mg twice daily (*P*<0.05, *P*<0.01 and *P*<0.001, respectively) but not with the HCTZ group (*P*>0.10). Sodium level did not alter during the various treatment periods when compared with the placebo period, or between the individual treatment periods (*P*>0.10). Potassium level fell significantly during the HCTZ period (*P*<0.001) and furosemide 25 mg and 40 mg twice daily period (*P*<0.01 and *P*<0.001, respectively). Potassium level was not significantly affected with furosemide 12.5 mg twice daily (*P*>0.10). Side effects including headache, dizziness, fatigue and nausea were more marked during the run-in period and placebo periods compared to the active treatment with high doses of drugs (*P* value not reported). Secondary: Not reported
Pupita et al[41] Furosemide 25 mg QD vs chlorthalidone 50 mg QD	RCT, XO Men and women with a mean age of 53.9±9.2 years with mild to moderate hypertension	N=36 12 months	Primary: Blood pressure Secondary: Plasma electrolytes, adverse events	Primary: Patients taking chlorthalidone had significantly lower SBP at each monthly measurement compared to baseline (*P*<0.01). However, only DBP values at month 5 were significant compared to baseline (*P*<0.05). Patients taking furosemide had significantly lower SBP at months 3, 4, and 5 compared to baseline (*P*<0.05 for month 3, and *P*<0.01 for months 4 and 5). DBP values were significantly lower at all monthly measurements compared to baseline in patients taking furosemide (*P*<0.01). At month 1, SBP decreased by 19.4 mm Hg with chlorthalidone and by 21.2 mm Hg with furosemide (*P*<0.001). DBP decreased by 11 mm Hg with chlorthalidone and by 12.6 mm Hg with furosemide at month 1 (*P*<0.001). Secondary: There were no significant changes in serum sodium levels with either

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				chlorthalidone or furosemide. Patients taking chlorthalidone had significantly lower serum chloride levels compared to baseline at all points (*P*<0.01), whereas patients taking furosemide had significantly lower levels only at month 6 (*P*<0.05). Both chlorthalidone and furosemide significantly reduced serum potassium levels at all points compared to baseline (*P*<0.01). Patient taking chlorthalidone reported adverse effects including dizziness, transient abdominal disorder, and slight weakness. Patients taking furosemide reported transient early weakness and irritability. The rate of adverse events was not statistically significant in either treatment group (*P* value not reported).
Araoye et al[42] Furosemide 40 mg BID vs HCTZ 50 mg BID	DB, XO Patients with hypertension	N=not specified 3 months	Primary: Blood Pressure Secondary: Not reported	Primary: Furosemide and HCTZ significantly reduced blood pressure (*P* value not reported). The decrease in blood pressure was consistently greater in the HCTZ group than with furosemide (*P* value not reported); however the difference was significant in regards to SBP only (*P* value not reported). Secondary: Not reported.
Bagshaw et al[43] Loop diuretics including frusemide[*], torasemide[†] vs placebo	MA RCT's comparing loop diuretics with control in patients with acute renal failure	N=555 Various	Primary: Mortality, need for renal replacement therapy, and renal recovery Secondary: Change to urine output, serum potassium level and acid-base status, duration of acute renal failure or renal replacement therapy, length of hospital stay, and toxicity	Primary: There was no statistical difference in mortality between loop diuretics compared to placebo (OR 1.28; 95% CI, 0.89 to 1.84; *P*=0.18). There was no statistical difference in renal recovery between loop diuretics and control (OR 0.88; 95% CI, 0.59 to 1.31; *P*=0.5). Secondary: Loop diuretics were associated with a shorter duration of renal replacement therapy (weighted mean difference of 1.4 days; 95% CI, 0.2 to 2.3; *P*=0.02), shorter time to spontaneous decline in serum creatinine level (weighted mean difference, 2.1 days; 95% CI, 0.4 to 3.7; *P*=0.01), and a greater increase in urine output from baseline (OR 2.6; 95% CI, 1.4 to 4.9; *P*=0.004). There was no data available on acid-base status, hospital status, hospital length of stay or health costs. Four studies reported toxicity, most commonly as transient tinnitus and deafness.
Galloe et al[44]	DB, double PC,	N=16	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bumetanide 0.5 mg (0,1,2 or 4 tablets twice daily) combined with trandolapril 0.5 mg (0,1,2, or 4 tablets once daily) to achieve 16 different dosage combinations	RCT, multiple XO Men and women with previous myocardial infarction at least 3 years ago, had medical treatment for heart failure and ejection fraction between 0.36 and 0.54 estimated by echo-cardiography (wall motion index)	14 days	Patient reported quality of life Secondary: Effects on the involved organs: kidney function, left ventricular function and blood pressure	Patient's well-being increased 12% with 0.5 mg bumetanide twice daily but higher doses bumetanide decreased patient's well-being by 12% compared to placebo (P<0.002). Increasing doses of bumetanide tended to increase tiredness (P=0.072). There were no statistically significant effects of bumetanide on the patient's opinion of their health, degree of dyspnea, appetite or work capacity. Secondary: Bumetanide increased 24-hour urine production in a straight dose-dependent manner (P<0.0001) while trandolapril had no effect (P=0.53). Bumetanide and trandolapril did not alter the 24-hour creatinine excretion and creatinine clearance (P=0.33, P=0.11 and P=0.53, P=0.97, respectively). Bumetanide decreased left ventricular function and increased heart rate in a dose dependent manner (P<0.001). Left ventricular function was also decreased with trandolapril but did not reach statistically significant. (P>0.062). Trandolapril significantly reduced SBP by maximally of 7.6 mm Hg (5.8%) with the lowest dose of 0.5 mg daily (P=0.007). Bumetanide had no significant effect on DBP (P=0.23).

*Synonym for furosemide.
† Synonym for torsemide.
Drug regimen abbreviations: BID=twice daily, IV, intravenous, PO=by mouth, QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, SC=single centre, SD=standard deviation, XO=crossover
Other abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, NYHA=New York Heart Association, PBV=pulmonary blood volume, PEV=pulmonary extravascular fluid volume, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Loop Diuretics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
bumetanide	injection, tablet	Bumex®*	$	$
ethacrynate sodium	injection	Edecrin Sodium®	$$$$	N/A
ethacrynic acid	tablet	Edecrin®	$$$$	N/A
furosemide	injection, solution, tablet	Lasix®*	$	$
torsemide	injection, tablet	Demadex®*	$$$$$	$$

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

X. Conclusions

There are currently 5 loop diuretics available on the market, bumetanide, ethacrynate sodium, ethacrynic acid, furosemide, and torsemide. All loop diuretics are Food and Drug Administration (FDA) approved for edema. Furosemide and torsemide are also FDA approved for the treatment of hypertension. Additionally, ethacrynate sodium and ethacrynic acid are FDA approved for acute treatment of congenital heart disease or the nephrotic syndrome in hospitalized pediatric patients, other than infants. Ethacrynic acid is less widely used due to the ototoxicity side effect when given at high doses and its relative insolubility makes it difficult to administer intravenously.[8] Ethacrynic acid is typically reserved for patients who are intolerable to furosemide and bumetanide

due to the sulfa allergy. Bumetanide, furosemide, and torsemide are all available generically in at least one dosage form or strength, while ethacrynate sodium and ethacrynic acid are only available as brand products.

The serious side effects associated with loop diuretics are electrolyte abnormalities, hypersensitivity reactions and ototoxicity.[8,20-26] Bumetanide, furosemide and torsemide can cause hypersensitivity reactions, manifested as a rash or rarely acute interstitial nephritis, which can be seen with other sulfonamide drugs.[8] Ethacrynic acid is the only loop diuretic that is not a sulfonamide derivative and can be safely used in patient with a sulfa allergy.[22] The incidence of ototoxicity is more common with high dose furosemide and concomitant use with an aminoglycoside.[23,24] According to a recent study by Rejnmark et al, use of loop diuretics was associated with an increased risk of any fractures including hip, spine and forearm especially with furosemide.[45] Another study confirmed that bumetanide affects bone turnover and decreases bone mineral density in osteopenic postmenopausal women.[46]

For the treatment of edema related to heart failure, the American College of Cardiology/American Heart Association (ACC/AHA), the Heart Failure Society of America (HFSA) and the European Society of Chronic Heart Failure recommend single entity diuretics.[5,17-19] Diuretics and salt restriction are indicated in patients with current or previous symptoms of heart failure and evidence of fluid retention due to reduced left ventricular ejection fraction.[17] Loop or thiazide diuretics in general are also recommended in patients with heart failure and volume overload, including those with normal left ventricular ejection fraction to control pulmonary congestion and peripheral edema.[17-18] In addition, the HFSA recommends that patients with acute decompensated heart failure (ADHF) and evidence of fluid overload be treated initially with loop diuretics, given intravenously rather than orally.[18] They also recommend that patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics.[18] A recent Cochrane review of diuretics for heart failure concludes that conventional diuretics including thiazide, loop, and potassium-sparing seem to reduce the risk of death and declining heart failure when compared to placebo, and diuretics appear to improve exercise capacity when compared to active control.[4] The major national guidelines including the Seventh Report of the JNC 7, the World Health Organization (WHO), the National Institute for Health and Clinical Excellence (NICE) and the Treatment Guidelines from the Medical Letter all recommend that a diuretic agent should be considered as initial therapy for the majority of patients who present with hypertension.[5,9,11-12] Although pharmacokinetic and pharmacodynamic differences exist between loop diuretics, the clinical relevance of these differences has not been established. A limited number of studies have been conducted comparing loop diuretics at adequate doses and duration to one another. Comparative data regarding loop diuretics has not demonstrated distinct, clinically significant differences regarding efficacy, safety and tolerability. The consensus guidelines do not give preference to or distinguish one loop diuretic over another.

All brand products, generics, and over-the-counter products within the class reviewed are comparable to each other in regards to efficacy and offer no significant clinical advantages for the management of hypertension and/or edema related to heart failure. Product selection should be based on the patient's diagnosis, incidence of side effects, comorbid conditions, and whether or not a sulfa allergy is present.

XI. Recommendations

No brand loop diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Potassium-sparing Diuretics
Single Entity Agents
AHFS Class 402816
September 10, 2008

I. Overview

The potassium-sparing diuretics work through direct inhibition of the sodium-potassium ion exchange at the distal convoluted tubule, cortical collecting tubule and collecting duct.[1,2] This inhibition results in reduced reabsorption of sodium, leading to reduced excretion of potassium and hydrogen.[3,4] The potassium-sparing diuretics are considered weak antihypertensives, with a maximum excretion of 1%-2% of the filtered sodium when used alone.[5] Amiloride is generally used in combination with thiazide or loop diuretics to provide an additive hypotensive effect, diminish the degree of potassium loss, and/or increase the net diuresis in patients with refractory edema.[5,6]

Since aldosterone stimulates the excretion of potassium, spironolactone and eplerenone, which inhibit aldosterone, also have potassium-sparing activity. However, they have been placed in a separate class, the Mineralocorticoid (Aldosterone) Receptor Antagonists by the American Hospital Formulary Service (AHFS). [7] Amiloride works through a different mechanism of action and their diuretic action is independent of aldosterone. [3]

The single entity potassium-sparing diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Single Entity Potassium-sparing Diuretics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
amiloride	tablet	Midamor®*†	amiloride

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the single entity potassium-sparing diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of congestive heart failure and hypertension please refer to the Appendix.

Table 2. Treatment Guidelines Using the Single Entity Potassium-sparing Diuretics

Clinical Guideline	Recommendation(s)
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[8]	<u>Patients at Risk for Developing Heart Failure (Stage A)</u> • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. <u>Patients With Current or Prior Symptoms of Heart Failure (Stage C)</u> • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. <u>Patients With Heart Failure and Normal Left Ventricular Ejection Fraction</u>

Clinical Guideline	Recommendation(s)
	• Diuretics are recommended to control pulmonary congestion and peripheral edema. Patients With Refractory End-Stage Heart Failure (Stage D) • Treatment of fluid retention is important.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)[9]**	Patients With Left Ventricular Systolic Dysfunction • An aldosterone antagonist may be added to the standard medication regimen (including diuretics) in patients who are in NYHA functional class IV or those in class III previously in class IV (left ventricular ejection fraction ≤35%) from left ventricular systolic dysfunction. • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics are typically preferred. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • Diuretics are recommended in patients with evidence of fluid overload. Patients With Acute Decompensated Heart Failure • Intravenous vasodilators, diuretics, and inotropes have all been used to treat patients with acute decompensated heart failure. Managing Patients With Heart Failure and Hypertension • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or calcium channel blocking agents (CCBs). • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)[10]**	• ACE inhibitors are recommended in patients with left ventricular ejection fraction 40%-45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention. • Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated. • Potassium-sparing diuretics are only recommended if hypokalemia persists despite ACE inhibition or in patients with severe heart failure who are already on a combination of an ACE inhibitor and low-dose spironolactone, or in patients who are intolerant to even low doses of spironolactone. • A combination of digoxin and a β-blocker seems to be more efficacious to either agent alone in patients with atrial fibrillation. Digoxin may reduce hospitalizations in patients with heart failure caused by left ventricular systolic dysfunction and sinus rhythm who are already treated with ACE inhibitors, β-blockers, diuretics, and spironolactone (in severe heart failure).
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)[11]**	• High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African

Clinical Guideline	Recommendation(s)
	American patients. • Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should not be used in patients whose potassium levels are greater than 5.0 mEq/L.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[12]	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[13]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics).
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[14]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients. • Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[15]	• If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker.
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[16]	• No specific recommendation is made concerning single entity potassium-sparing diuretics.
American Diabetes Association (ADA): **Standards of Medical Care in**	• No specific recommendation is made concerning single entity potassium-sparing diuretics.

Clinical Guideline	Recommendation(s)
Diabetes—2008[17]	
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[18]	• Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[19]	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence.

III. Indications

FDA-approved indications for the single entity potassium-sparing diuretics 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 Single Entity Potassium-sparing Diuretics[1]

Drug	Indication
Amiloride	Adjunctive treatment with thiazide diuretics or other kaliuretic diuretic agents in congestive heart failure or hypertension: (a) to help restore normal serum potassium levels in patients who develop hypokalemia on the kaliuretic diuretic (b) to prevent development of hypokalemia in patients who would be exposed to particular risk if hypokalemia were to develop, eg, digitalized patients or patients with significant cardiac arrhythmias.

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity potassium-sparing diuretics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Single Entity Potassium-sparing Diuretics[1,20,21]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Amiloride	30-90	23	Excreted unchanged by the kidneys	None	50	Urine, stool	6-9

V. Drug Interactions

Significant drug interactions with the single entity potassium-sparing diuretics are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Single Entity Potassium-sparing Diuretics[22]

Drug(s)	Significance Level	Interaction	Mechanism
Potassium-sparing diuretics (amiloride)	1	Angiotensin converting enzyme (ACE) inhibitors (all)	Combining ACE inhibitors and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high-risk (eg, renally impaired) patients. The mechanism is unknown.
Potassium-sparing diuretics (amiloride)	1	Angiotensin II receptor antagonists (ARBs) (all)	Combining ARBs and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high-risk (eg, renally impaired, type 2 diabetic) patients, leading to an additive or synergistic effect.
Potassium-sparing diuretics (amiloride)	1	Eplerenone	Potassium-sparing diuretics reduce the renal elimination of potassium ions, therefore increasing potassium retention, which may increase the risk of hyperkalemia and associated serious, sometimes fatal arrhythmias.
Potassium-sparing diuretics (amiloride)	1	Potassium supplements (acetate, acid phosphate, bicarbonate, chloride, citrate, gluconate, iodide, and phosphate salts of potassium)	Potassium-sparing diuretics will increase potassium retention and can produce severe hyperkalemia.
Potassium-sparing diuretics (amiloride)	1	Quinidine	Combining quinidine and potassium-sparing diuretics may contribute to proarrhythmia due to potential synergistic increase in myocardial sodium channel blockade.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse reactions reported with the single entity potassium-sparing diuretics are noted in Table 6. Additionally, details of the black box warning regarding the risk of hyperkalemia with amiloride can be found in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Single Entity Potassium-sparing Diuretics[1]

Adverse Event(s)	Amiloride
Cardiovascular	
Angina pectoris	≤1
Arrhythmia	≤1
Orthostatic hypotension	≤1
Palpitation	≤1
Central Nervous System	
Decreased libido	≤1

Adverse Event(s)	Amiloride
Depression	≤1
Dizziness	>1
Encephalopathy	>1
Insomnia	≤1
Mental Confusion	≤1
Nervousness	≤1
Paresthesia	≤1
Somnolence	≤1
Tremors	≤1
Vertigo	≤1
Dermatological	
Alopecia	≤1
Dryness of mouth	≤1
Itching	≤1
Pruritus	≤1
Skin rash	≤1
Endocrine and Metabolic	
Elevated serum potassium levels (>5.5 mEq per liter)	✔
Gastrointestinal	
Abdominal fullness	≤1
Abdominal pain	>1
Appetite changes	>1
Constipation	>1
Diarrhea	3-8
Dyspepsia	≤1
Flatulence	≤1
Gas pain	>1
Gastrointestinal bleeding	≤1
Gastrointestinal disturbance	≤1
Heartburn	≤1
Jaundice	≤1
Nausea/anorexia	3-8
Thirst	≤1
Vomiting	3-8
Genitourinary	
Bladder spasms	≤1
Dysuria	≤1
Gynecomastia	≤1
Impotence	>1
Polyuria	≤1
Urinary frequency	≤1
Musculoskeletal	
Joint pain	≤1
Leg ache	≤1
Muscle cramps	>1
Respiratory	
Cough	>1
Dyspnea	>1
Shortness of breath	≤1
Other	
Back pain	≤1
Chest pain	≤1

Adverse Event(s)	Amiloride
Fatigability	>1
Headache	3-8
Increased intraocular pressure	≤1
Nasal congestion	≤1
Neck/shoulder ache	≤1
Pain, extremities	≤1
Tinnitus	≤1
Visual disturbances	≤1
Weakness	>1

- Event not reported or incidence <1%.
✓ Percent not specified.

Table 7. Black Box Warning for Amiloride[1]

Hyperkalemia
Like other potassium-conserving agents, amiloride may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) which, if uncorrected, is potentially fatal. Hyperkalemia occurs commonly (about 10%) when amiloride is used without a kaliuretic diuretic. This incidence is greater in patients with renal impairment, diabetes mellitus (with or without recognized renal insufficiency), and in the elderly. When MIDAMOR is used concomitantly with a thiazide diuretic in patients without these complications, the risk of hyperkalemia is reduced to about 1%-2%. It is thus essential to monitor serum potassium levels carefully in any patient receiving amiloride, particularly when it is first introduced, at the time of diuretic dosage adjustments, and during any illness that could affect renal function.

VII. Dosing and Administration

The usual dosing regimens for the single entity potassium-sparing diuretics are summarized in Table 8.

Table 8. Usual Dosing for the Single Entity Potassium-sparing Diuretics[1]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amiloride	Tablet: initial, 5 mg daily; maintenance, 5 mg daily, may increase to 10 mg daily if needed; maximum, the dose can be increased to 15 mg, then 20 mg, if persistent hypokalemia is documented	Safety and efficacy in children have not been established.	Tablet: 5 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity potassium-sparing diuretics are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Single Entity Potassium-sparing Diuretics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Heart Failure				
Faris et al[23] One diuretic (loop diuretics [furosemide, bumetanide], thiazide diuretics [chlorothiazide], or potassium-sparing diuretics [amiloride, triamterene]) vs placebo or with open control or one diuretic (loop diuretics [furosemide, bumetanide], thiazide diuretics [chlorothiazide], or potassium-sparing diuretics [amiloride, triamterene]) vs another active agent (eg, angiotensin converting enzyme inhibitors, digoxin)	MA 14 double-blinded, randomized control trials of diuretic therapy comparing loop, thiazide, or potassium-sparing diuretics with placebo or with open control; or one diuretic with another active agent in adult patients with chronic heart failure	N=525 2 to 52 weeks	Primary: Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Primary: Mortality was reported in 3 of the 7 placebo-controlled trials, and this analysis showed that mortality was lower for patients treated with diuretics than with placebo (3/111[2.7%] vs 12/110 [10.9%], respectively; OR 0.24; 95% CI, 0.07 to 0.83; *P*=0.02). These results showed that patients treated with diuretics had an absolute risk reduction of 8% when compared to placebo and a number needed to treat of 12.5. Secondary: An analysis of pooled data from 2 trials showed lower admission rates for worsening heart failure in patients taking diuretics than in patients taking placebo (OR 0.07; 95% CI, 0.01 to 0.52; *P*=0.01). Diuretics were found to improve exercise capacity, with a difference in means of 0.74 (95% CI, 0.37 to 1.11; *P*<0.0001) and of 0.67 (95% CI, 0.02 to 1.31; *P*=0.04.), respectively. The combined results of these 4 trials indicated that diuretics improved exercise capacity in participants with chronic heart failure with a difference in means of 0.72 (95% CI, 0.40 to 1.04; *P*<0.0001).
Bayliss et al[24] Amiloride 5 mg QD and furosemide 40 mg (combination	OS Patients with heart failure, 22	N=12 1 month	Primary: Average weight, heart rate at rest and maximal	Primary: Average weight was significantly reduced during treatment from 72.4 to 68.5 kg (*P*=0.0003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
entity)	to 75 years of age, referred with breathlessness on moderate exertion (NYHA class II-III) who were not previously treated		exercise, maximal treadmill exercise time, plasma renin, plasma aldosterone, noradrenaline at rest and maximal exercise Secondary: Not reported	Resting heart rate decreased from 89 to 75 bpm (*P*=0.03). There was no significant change during exercise (*P* value not reported). Maximal treadmill exercise time significantly increased from 9.1 to 17.6 minutes (*P*=0.007). Plasma concentrations of renin increased from 1.1 to 4.2 ng/mL/hr at rest and from 2.5 to 11.3 ng/mL/hr upon exercise (*P*<0.007). Plasma concentrations of aldosterone increased from 169 to 488 pmol/L at rest and from 223 to 737 pmol/L upon exercise (*P*<0.007). Plasma concentrations of noradrenaline were significantly reduced (decreased to within normal ranges) at rest following treatment (*P*=0.005) but remained abnormally high at maximal exercise following treatment. Secondary: Not reported
Rengo et al[25] Amiloride 15 mg QD vs amiloride 15 mg QD and HCTZ 150 mg QD (combination entity) vs HCTZ 150 mg QD	RCT Patients 35 to 60 years of age with liver cirrhosis and ascites or congestive heart failure	N=30 15 days	Primary: Body weight, 24 hour diuresis, serum sodium, serum potassium, sodium and potassium urinary loss Secondary: Not reported	Primary: All groups had a statistically significant reduction in body weight from baseline (*P*<0.001, all groups). Combination amiloride-HCTZ showed a significantly greater reduction compared to amiloride alone (*P*<0.001). All groups significantly differed from baseline in 24 hour diuresis (*P*<0.01). Amiloride-HCTZ and HCTZ resulted in more diuresis than amiloride (*P*<0.001, for both). Serum sodium was reduced from baseline in all groups. HCTZ alone had a significantly greater reduction than amiloride (*P*<0.01), and amiloride-HCTZ (*P*<0.001). Sodium urinary loss was seen in all treatments at day 2, amiloride-HCTZ had maintained this loss at day 5 (*P*<0.001, for both). Serum potassium decreased in the HCTZ group but increased in the amiloride and amiloride-HCTZ groups. HCTZ alone resulted in a marked increase in potassium urinary loss (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Cheitlin et al[26] Amiloride 5 or 10 mg QD for 7 days, placebo QD for the next 14 days, along with HCTZ 50 or 100 mg QD (separate entities) vs placebo QD for 14 days, amiloride 5 or 10 mg QD for the next 7 days, along with HCTZ 50 or 100 mg QD (separate entities)	DB, PC, RCT, XO Patients with an average age of 63 and a history of congestive heart failure and ≥1 episode of pulmonary edema (NYHA class II-III) who were not previously treated	N=11 21 days	Primary: Hemodynamic changes at rest and exercise Secondary: Not reported	Primary: At rest, there were no significant differences between patients treated with placebo or amiloride in right atrial pressure, pulmonary atrial pressure, heart rate, pulmonary artery wedge pressure, systemic arterial pressure, right ventricular stroke work index, left ventricular stroke work index, systemic vascular resistance, cardiac index, or stroke volume index (*P* values not reported). During exercise, there were significant differences between patients treated with placebo or amiloride at the 50-watt stage in right atrial pressure (15.0 vs 10.5 mm Hg), pulmonary artery wedge pressure (28.6 vs 22.1 mm Hg), pulmonary artery diastolic pressure (32.2 vs 21.6 mm Hg), mean pulmonary artery pressure (44.4 vs 38.9 mm Hg), left ventricular stroke work index (69.5 vs 77.9 g-m/m^2), and stroke volume index (44.9 vs 46.2 cc/beat/m^2), respectively (*P* values not reported). There were no significant differences between placebo and amiloride during exercise in right ventricular stroke work index, heart rate, aortic pressure, cardiac index, and total systemic vascular resistance (*P* values not reported). Secondary: Not reported
Hypertension				
Salmela et al[27] Amiloride 2.5 mg plus HCTZ 25 mg daily vs HCTZ 25 mg daily	DB, MC, PG, RCT Men and women with mild to moderate hypertension, mean 66.7 years of age	N=40 12 weeks	Primary: Changes in blood pressure Secondary: Not reported	Primary: At the end of the first treatment period, mean supine SBP and DBP was 161 and 91 mm Hg for subjects receiving combination treatment; from baseline week 4; *P*<0.01 and *P*<0.001, respectively. At the end of the first treatment period, mean supine SBP and DBP was 165 and 96 mm Hg for subjects receiving HCTZ monotherapy; *P*<0.01, from baseline week 4 to the end of the first treatment period. At the end of the second treatment period, mean supine SBP and DBP was 154 and 86 mm Hg for subjects receiving combination treatment; from baseline week 4 to the end of the second treatment period; *P*<0.01 and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.001. At the end of the second treatment period, mean supine SBP and DBP was 155 and 90 mm Hg for subjects receiving HCTZ monotherapy; for both; *P*<0.001 from baseline week 4 to the end of the second treatment period. There were no statistically significant differences in blood pressure reduction between the 2 groups; *P* value not reported. Secondary: Not reported
Multicenter Diuretic Cooperative Study Group[28] Amiloride 5 mg QD vs amiloride 5 mg and HCTZ 50 mg QD (combination entity) vs HCTZ 50 mg QD	DB, MC, RCT Patients 21 to 69 years of age with mild to moderate essential hypertension (supine DBP 95 to 115 mm Hg)	N=179 12 weeks	Primary: Change from baseline in average supine SBP and DBP Secondary: Heart rate, body weight, serum potassium	Primary: Baseline vs 12-week average supine blood pressure was 153/101 vs 139/93 mm Hg for amiloride, 160/100 vs 137/90 mm Hg for amiloride-HCTZ, and 154/101 vs 134/89 mm Hg for HCTZ. Reductions in supine blood pressure was significant in all treatment groups (*P*<0.01). The SBP reduction was greater with amiloride-HCTZ than with amiloride at all weeks and HCTZ at 4 and 8 weeks (*P*<0.05, both). Secondary: No significant changes from baseline in heart rate were observed with amiloride or HCTZ (*P* values not reported). An increase in heart rate was observed with amiloride-HCTZ of 3.3 bpm (*P*<0.05). Changes in body weight from baseline were –1.17 kg for amiloride-HCTZ, –0.72 kg for HCTZ, and 0.045 kg for amiloride (*P*<0.05, for amiloride-HCTZ only). Changes in serum potassium from baseline were 0.23 mEq/L for amiloride (*P*<0.01), –0.38 mEq/L for amiloride-HCTZ (*P*<0.01), and –0.59 mEq/L for HCTZ (*P*<0.01). The HCTZ change was statistically greater than the amiloride-HCTZ change (*P*<0.05). 23% of HCTZ, 2% of amiloride-HCTZ, and 0% of amiloride patients experienced hypokalemia.
Kohvakka, Eisalo, et al[29] Amiloride 5 mg QD in patients receiving HCTZ 50 mg QD	PC, RCT, XO Patients 41 to 70 years of age with	N=31 3 months	Primary: Changes in blood pressure, serum potassium,	Primary: No significant changes in blood pressure were observed with any of the treatment groups (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(combination entity) vs triamterene 75 mg QD in patients receiving HCTZ 50 mg QD (combination entity) vs KCl 1,500 mg QD in patients receiving HCTZ 50 mg QD (separate entities) vs spironolactone 50 mg QD in patients receiving HCTZ 50 mg QD (separate entities) vs placebo	uncomplicated hypertension, previously treated with antihypertensive agents for 1 to 6 years		sodium, creatinine, urate, total body potassium Secondary: Not reported	Mean serum potassium was reduced in all active treatment groups except with the spironolactone group. KCl supplementation was least effective in elevating serum potassium. Total body potassium remained constant throughout treatment (*P* values not reported). Serum sodium remained within normal limits in all treatment groups (*P* values not reported). There were no significant changes in mean serum creatinine in any of the treatment groups (*P* values not reported). Serum urate concentration increased significantly in all treatment groups including HCTZ alone (*P* values not reported). Secondary: Not reported

Drug regimen abbreviations: HCTZ=hydrochlorothiazide, KCl=potassium chloride, QD=once daily
Study abbreviations: DB=double-blind, MA=metaanalysis, MC=multicenter, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Miscellaneous abbreviations: bpm=beats per minute, DBP=diastolic blood pressure, NYHA=New York Heart Association, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Single Entity Potassium-sparing Diuretics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
amiloride	tablet	Midamor®*†	N/A	$$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

Amiloride, available as a generic, is the only potassium-sparing diuretic discussed in this review. Clinical studies have demonstrated the safety and efficacy of amiloride for the treatment of hypertension, edematous conditions, and preventing serum potassium loss in patients taking thiazide or loop diuretics. In many of these studies, amiloride was not used as a single agent, but in combination with a thiazide or loop diuretic.[23-29]

Amiloride should not be used as a first-line antihypertensive agent or in place of thiazide diuretics, which are considered first-line agents for the treatment of hypertension in patients who do not have other significant comorbid conditions. As monotherapy, amiloride is considered a weak antihypertensive; therefore, it is rarely used alone. The primary role of amiloride is in combination with a loop or thiazide diuretic to provide an additive hypotensive effect, to minimize potassium excretion, thereby preventing diuretic-induced hypokalemia in patients being treated for hypertension and edematous conditions. The current hypertension and heart failure guidelines include amiloride as a potassium-sparing diuretic for adjunctive therapy.[8-19] Combining angiotensin converting enzyme inhibitors or angiotensin receptor blockers with potassium-sparing diuretics may result in elevated serum

potassium concentrations in certain high patients, leading to an additive or synergistic effect. As such, caution should be advised.

Therefore, all products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity potassium-sparing diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Potassium-sparing Diuretics Combination Products
AHFS Class 402816
September 10, 2008

I. Overview

This review includes potassium-sparing diuretic and hydrochlorothiazide combination products. The potassium-sparing diuretics work through direct inhibition of the sodium-potassium ion exchange at the distal convoluted tubule, cortical collecting tubule and collecting duct.[1,2] The inhibition can lead to hyperkalemia and metabolic acidosis from the concurrent reductions in potassium and hydrogen ion excretion.[3,4] The potassium-sparing diuretics are considered weak antihypertensives with a maximum excretion of 1%-2% of the filtered sodium when used alone.[5] They provide an additive hypotensive effect, diminish the degree of potassium loss, and/or increase the net diuresis in patients with refractory edema when they are used in combination with a thiazide diuretic.[5,6]

Hydrochlorothiazide is a thiazide diuretic and increases the excretion of sodium and chloride by inhibiting reabsorption in the distal tubule, the connecting segment at the end of the distal tubule, and possibly the early cortical collecting duct.[5] The combination diuretics are both Food and Drug Administration (FDA) approved for hypertension in patients who develop hypokalemia with thiazide or other kaliuretic diuretics or cannot risk hypokalemia with thiazide diuretics alone. Additionally, amiloride and hydrochlorothiazide is FDA approved for congestive heart failure and triamterene and hydrochlorothiazide is FDA approved for edema. They are not used as initial therapy and are typically used in combination with other antihypertensives.[3-5]

The combination diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Combination Potassium-sparing Diuretics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
amiloride and hydrochlorothiazide	tablet	Moduretic®*	Moduretic®*, amiloride and hydrochlorothiazide
triamterene and hydrochlorothiazide	capsule, tablet	Dyazide®*, Maxzide®*	triamterene and hydrochlorothiazide

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the combination potassium-sparing diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of congestive heart failure and hypertension please refer to the Appendix.

Table 2. Treatment Guidelines Using the Combination Potassium-Sparing Diuretics

Clinical Guideline	Recommendation(s)
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[7]	• Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. <u>Patients With Current or Prior Symptoms of Heart Failure (Stage C)</u> • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have

Clinical Guideline	Recommendation(s)
	evidence of fluid retention. <u>Patients With Heart Failure and Normal Left Ventricular Ejection Fraction</u> • Diuretics are recommended to control pulmonary congestion and peripheral edema. <u>Patients With Refractory End-Stage Heart Failure (Stage D)</u> • Treatment of fluid retention is important.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)[8]**	<u>Patients With Left Ventricular Systolic Dysfunction</u> • An aldosterone antagonist may be added to the standard medication regimen (including diuretics) in patients who are in NYHA functional class IV or those in class III previously in class IV (left ventricular ejection fraction ≤35%) from left ventricular systolic dysfunction. • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics are typically preferred. <u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u> • Diuretics are recommended in patients with evidence of fluid overload. <u>Patients With Acute Decompensated Heart Failure</u> • Intravenous vasodilators, diuretics, and inotropes have all been used to treat patients with acute decompensated heart failure. <u>Managing Patients With Heart Failure and Hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or calcium channel blocking agents (CCBs). • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)[9]**	• ACE inhibitors are recommended in patients with left ventricular ejection fraction 40%-45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention. • Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated. • Potassium-sparing diuretics are only recommended if hypokalemia persists despite ACE inhibition or in patients with severe heart failure who are already on a combination of an ACE inhibitor and low-dose spironolactone, or in patients who are intolerant to even low doses of spironolactone. • Aldosterone antagonists are recommended in addition to ACE inhibitors, β-blockers, and diuretics in patients who have advanced heart failure (NYHA class III-IV) with systolic dysfunction, and in patients who are unable to tolerate therapy with ACE inhibitors.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)[10]**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial

Clinical Guideline	Recommendation(s)
	treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia. • Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should not be used in patients whose potassium levels are greater than 5.0 mEq/L.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[11]	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[12]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following

Clinical Guideline	Recommendation(s)
	should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[13]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients. • Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[14]	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes).
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[15]	• No specific recommendation is made concerning combination potassium-sparing diuretics.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[16]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2. • Multiple drug therapy is generally required to achieve blood pressure goals.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[17]	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[18]	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-

Clinical Guideline	Recommendation(s)
	blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence. • Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible.

III. Indications

FDA-approved indications for the combination potassium-sparing diuretics 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 Combination Potassium-sparing Diuretics[19-22]

Indication	Amiloride and Hydrochlorothiazide	Triamterene and Hydrochlorothiazide
Patients with hypertension or with congestive heart failure who develop hypokalemia when thiazides or other kaliuretic diuretics are used alone, or in whom maintenance of normal serum potassium levels is considered clinically important (i.e., digitalized patients or patients with significant cardiac arrhythmias)	✔	
Patients with hypertension or edema who develop hypokalemia on hydrochlorothiazide alone or those that require a thiazide diuretic and in whom the development of hypokalemia cannot be risked		✔

IV. Pharmacokinetics

The pharmacokinetic parameters for the combination potassium-sparing diuretics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Combination Potassium-sparing Diuretics[19-26]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Amiloride	30-90	23	Excreted unchanged by the kidneys	None	50	Urine, stool	6-9
Triamterene	30-70	55-67	Hepatic	Hydroxy-triamterene	21	Urine	1.5-2.5

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
				sulfate			
Hydrochlorothiazide	50-75	40-68	Not appreciably metabolized	Not reported	>95	Urine	6-15

V. Drug Interactions

Significant drug interactions with the combination potassium-sparing diuretics are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Combination Potassium-sparing Diuretics[27]

Drug(s)	Significance Level	Interaction	Mechanism
Potassium-sparing diuretics (amiloride, triamterene)	1	Angiotensin converting enzyme (ACE) inhibitors (all)	Combining ACE inhibitors and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high risk (eg, renally impaired) patients. The mechanism is unknown.
Potassium-sparing diuretics (amiloride, triamterene)	1	Angiotensin II receptor antagonists (ARBs) (all)	Combining ARBs and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high risk (eg, renally impaired, type 2 diabetes) patients, leading to an additive or synergistic effect.
Potassium-sparing diuretics (amiloride, triamterene)	1	Eplerenone	Potassium-sparing diuretics reduce the renal elimination of potassium ions, therefore will increase potassium retention, which may increase the risk of hyperkalemia and associated serious, sometimes fatal arrhythmias.
Potassium-sparing diuretics (amiloride, triamterene)	1	Potassium supplements (acetate, acid phosphate, bicarbonate, chloride, citrate, gluconate, iodide, and phosphate salts of potassium)	Potassium-sparing diuretics will increase potassium retention and can produce severe hyperkalemia.
Potassium-sparing diuretics (amiloride, triamterene)	1	Quinidine	Combining quinidine and potassium-sparing diuretics may contribute to proarrhythmia due to potential synergistic increase in myocardial sodium channel blockade.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Thiazides (chlorothiazide, hydrochlorothiazide,	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be

Drug(s)	Significance Level	Interaction	Mechanism
methyclothiazide)			avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate carefully in small or intermittent doses.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse reactions reported with the combination potassium-sparing diuretics are noted in Table 6. Additionally, details of the black box warning regarding the risk of hyperkalemia with amiloride can be found in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Combination Potassium-sparing Diuretics[19-21]

Adverse Event(s)	Amiloride and Hydrochlorothiazide	Triamterene and Hydrochlorothiazide
Cardiovascular		
Angina pectoris	≤1	-
Arrhythmia	1-3	✔
Digitalis toxicity	≤1	-
Orthostatic hypotension	≤1	✔
Tachycardia	≤1	-
Central Nervous System		
Dizziness	3-8	✔
Depression	≤1	-
Insomnia	≤1	-
Mental Confusion	≤1	-
Nervousness	≤1	-
Paresthesia/numbness	≤1	✔
Sleepiness	≤1	-
Stupor	≤1	-
Vertigo	≤1	✔
Dermatological		
Alopecia	≤1	-
Diaphoresis	≤1	-
Erythema multiforme	≤1	-
Exfoliative dermatitis	≤1	-
Flushing	≤1	-
Pruritus	1-3	✔

Adverse Event(s)	Amiloride and Hydrochlorothiazide	Triamterene and Hydrochlorothiazide
Rash	3-8	✔
Endocrine and Metabolic		
Dehydration	≤1	-
Elevated serum potassium levels (>5.5 mEq per liter)	✔	✔
Gout	≤1	-
Symptomatic hyponatremia	≤1	-
Gastrointestinal		
Abdominal fullness	≤1	-
Abdominal pain	1-3	✔
Anorexia	≤1	-
Appetite changes	≤1	-
Constipation	≤1	✔
Diarrhea	1-3	✔
Flatulence	≤1	-
Gastrointestinal bleeding	≤1	-
Gastrointestinal disturbance	≤1	-
Gastrointestinal pain	1-3	-
Hiccups	≤1	-
Nausea/anorexia	3-8	✔
Thirst	≤1	-
Vomiting	≤1	✔
Genitourinary		
Dysuria	≤1	-
Gynecomastia	≤1	-
Impotence	≤1	✔
Incontinence	≤1	-
Nocturia	≤1	-
Renal dysfunction	≤1	✔
Musculoskeletal		
Joint pain	≤1	-
Leg ache	1-3	-
Muscle cramps/spasms	≤1	✔
Respiratory		
Dyspnea	1-3	✔
Other		
Back pain	≤1	-
Bad taste	≤1	-
Chest pain	≤1	-
Fatigue/tiredness	1-3	✔
Headache	3-8	✔
Malaise	≤1	-
Nasal congestion	≤1	-
Syncope	≤1	-
Visual disturbance	≤1	✔
Weakness	3-8	✔

- Event not reported or incidence <1%.
✔ Percent not specified.

Table 7. Black Box Warning for Amiloride[1]

Hyperkalemia
Like other potassium-conserving agents, amiloride may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) which, if uncorrected, is potentially fatal. Hyperkalemia occurs commonly (about 10%) when amiloride is used

Hyperkalemia
without a kaliuretic diuretic. This incidence is greater in patients with renal impairment, diabetes mellitus (with or without recognized renal insufficiency), and in the elderly. When MIDAMOR is used concomitantly with a thiazide diuretic in patients without these complications, the risk of hyperkalemia is reduced to about 1%-2%. It is thus essential to monitor serum potassium levels carefully in any patient receiving amiloride, particularly when it is first introduced, at the time of diuretic dosage adjustments, and during any illness that could affect renal function.

VII. Dosing and Administration

The usual dosing regimens for the combination potassium-sparing diuretics are summarized in Table 8.

Table 8. Usual Dosing for the Combination Potassium-sparing Diuretics[19-21]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amiloride and hydrochlorothiazide	Tablet: initial, 5/50 mg once daily; maintenance, 5/50 to 10/100 mg once daily or in divided doses	Safety and efficacy in children have not been established.	Tablet: 5 mg - 50 mg
Triamterene and hydrochlorothiazide	Tablet: initial, 37.5/25 mg once daily; maintenance: 37.5/25 to 75/50 mg once daily	Safety and efficacy in children have not been established.	Capsule: 37.5 mg - 25 mg 50 mg - 25 mg Tablet: 37.5 mg - 25 mg 75 mg - 50 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the combination potassium-sparing diuretics are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Combination Potassium-sparing Diuretics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Heart Failure				
Rengo et al[28] Amiloride 15 mg QD vs amiloride 15 mg QD and HCTZ 150 mg QD (combination entity) vs HCTZ 150 mg QD	RCT Patients 35 to 60 years of age with liver cirrhosis and ascites or congestive heart failure	N=30 15 days	Primary: Body weight, 24 hour diuresis, serum sodium, serum potassium, sodium and potassium urinary loss Secondary: Not reported	Primary: All groups had a statistically significant reduction in body weight from baseline (*P*<0.001, all groups). Combination amiloride-HCTZ showed a significantly greater reduction compared to amiloride alone (*P*<0.001). All groups significantly differed from baseline in 24 hour diuresis (*P*<0.01). Amiloride-HCTZ and HCTZ resulted in more diuresis than amiloride (*P*<0.001, for both). Serum sodium was reduced from baseline in all groups. HCTZ alone had a significantly greater reduction than amiloride (*P*<0.01), and amiloride-HCTZ (*P*<0.001). Sodium urinary loss was seen in all treatments at day 2, amiloride-HCTZ had maintained this loss at day 5 (*P*<0.001, for both). Serum potassium decreased in the HCTZ group but increased in the amiloride and amiloride-HCTZ groups. HCTZ alone resulted in a marked increase in potassium urinary loss (*P*<0.001). Secondary: Not reported
Kohvakka[29] Amiloride 5 mg BID in patients receiving HCTZ 50 mg BID (combination entity) vs	RCT, XO Patients 41 to 69 years of age with congestive heart failure(NYHA class II-III), average cardiac failure duration of 9.3 years, average previous diuretic	N=25 5 months	Primary: Changes in weight, blood pressure, serum sodium, serum potassium, total body potassium Secondary:	Primary: Weight loss was statistically significant in the amiloride-HCTZ and triamterene-HCTZ groups (*P*=0.05, both groups) but not in the KCl-HCTZ group (*P* value not reported) compared to HCTZ alone. No statistically significant changes in blood pressure were observed (*P* values not reported). No statistically significant differences in serum sodium were observed in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
triamterene 75 mg BID in patients receiving HCTZ 50 mg BID (combination entity) vs KCl 1 g BID in patients receiving HCTZ 50 mg BID (separate entities) vs HCTZ 50 mg BID	treatment duration of 6.8 years, developed persistent hypokalemia on HCTZ alone		Percentage with hypokalemia, median days until hypokalemia detection, serum magnesium	the amiloride-HCTZ or triamterene-HCTZ groups (*P* values not reported). Serum sodium was slightly higher in the KCl-HCTZ group (*P*=0.01) compared to HCTZ alone. Serum potassium was found to be significantly higher in all treatment groups compared to HCTZ alone (*P*=0.01, for all groups). Total body potassium was significantly higher with amiloride-HCTZ and triamterene-HCTZ (*P*=0.05, both groups) but not with KCl-HCTZ (*P* value not reported) compared to HCTZ alone. Secondary: The percentages of patients that became hypokalemic were 39% in the amiloride-HCTZ group, 52% in the triamterene-HCTZ group, and 52% in KCl-HCTZ group (*P* values not reported). The median days until hypokalemia detection were 114 for amiloride-HCTZ, 75 for triamterene-HCTZ, and 51.5 for KCl-HCTZ (*P* values not reported). Serum magnesium was maintained at a statistically higher rate with amiloride-HCTZ and triamterene-HCTZ than with KCl-HCTZ (*P* values not reported).
Cheitlin et al[30] Amiloride 5 or 10 mg QD for 7 days, placebo QD for the next 14 days, along with HCTZ 50 or 100 mg QD (separate entities) vs placebo QD for 14 days, amiloride 5 or 10 mg QD for the next 7 days, along with HCTZ 50 or	DB, PC, RCT, XO Patients with an average age of 63 and a history of congestive heart failure and ≥1 episode of pulmonary edema (NYHA class II-III) who were not previously treated	N=11 21 days	Primary: Hemodynamic changes at rest and exercise Secondary: Not reported	Primary: At rest, there were no significant differences between patients treated with placebo or amiloride in right atrial pressure, pulmonary atrial pressure, heart rate, pulmonary artery wedge pressure, systemic arterial pressure, right ventricular stroke work index, left ventricular stroke work index, systemic vascular resistance, cardiac index, or stroke volume index (*P* values not reported). During exercise, there were significant differences between patients treated with placebo or amiloride at the 50-watt stage in right atrial pressure (15.0 vs 10.5 mm Hg), pulmonary artery wedge pressure (28.6 vs 22.1 mm Hg), pulmonary artery diastolic pressure (32.2 vs 21.6 mm Hg), mean pulmonary artery pressure (44.4 vs 38.9 mm Hg), left ventricular stroke work index (69.5 vs 77.9 g-m/m^2), and stroke volume index (44.9 vs 46.2 cc/beat/m^2), respectively (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
100 mg QD (separate entities)				There were no significant differences between placebo and amiloride during exercise in right ventricular stroke work index, heart rate, aortic pressure, cardiac index, and total systemic vascular resistance (*P* values not reported). Secondary: Not reported
Ghosh et al[31] Amiloride 2.5 mg QD and HCTZ 25 mg QD (combination entity) vs triamterene 50 mg QD and HCTZ 25 mg QD (combination entity)	PG, RCT, SB Elderly patients (mean age 80) with stable, mild to moderate congestive heart failure	N=60 8 weeks	Primary: Body weight, clinical score, biochemistry Secondary: Not reported	Primary: Body weight was reduced in both treatment groups (*P* values not reported). Both treatments resulted in improvements in clinical scores; 95% of the amiloride-HCTZ group and 88% of the triamterene-HCTZ group showed an improvement in heart failure signs with no patient's symptoms becoming worse (*P* values were not reported). 85% of the amiloride-HCTZ group and 84% of the triamterene-HCTZ group showed an improvement in heart failure symptoms (*P* values were not reported). There were no significant between group differences in serum sodium, potassium, or urea (*P* values were not reported). Secondary: Not reported
Hypertension				
Larochelle et al [32] HCTZ 50 mg vs amiloride 5 mg and HCTZ 50 mg	DB, RCT Ambulant patients, 18 to 70 years of age with essential hypertension who after not being treated for at least 2 weeks prior to the study had a supine DBP of 95 to 109 mm Hg and a serum potassium level	N=266 8 weeks	Primary: Blood pressure and serum potassium concentration Secondary: Not reported	Primary: At 8 weeks, there were no statistically significant differences between groups in the mean blood pressure reductions (*P* value not reported). During the 8 weeks of treatment, the group receiving combination therapy experienced a decrease in the mean supine blood pressure and mean serum potassium level. Respectively these reductions were from 156/99 to 138/88 mm Hg and from 4.23 to 3.91 mmol/L. During the 8 weeks of treatment, the monotherapy group experienced a reduction in the mean supine blood pressure and mean serum potassium

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	of >3.5 mmol/L			level; respectively from 157/99 to 138/87 mm Hg and from 4.16 to 3.69 mmol/L. Hypokalemia occurred less frequently in the combination group than in the monotherapy group (14% and 29%; *P*=0.0026). However, the proportions of patients with a potassium level exceeding 4.5 mmol/L were similar 4.5% and 3.9%, respectively (*P* value not reported). Secondary: Not reported
Salmela et al[33] HCTZ 25 mg daily vs amiloride 2.5 mg plus HCTZ 25 mg daily	DB, MC, PG, RCT Men and women with mild to moderate hypertension, mean 66.7 years of age	N=40 12 weeks	Primary: Changes in blood pressure Secondary: Not reported	Primary: At the end of the first treatment period, mean supine SBP and DBP was 161 and 91 mm Hg for subjects receiving combination treatment; from baseline week 4; *P*<0.01 and *P*<0.001, respectively. At the end of the first treatment period, mean supine SBP and DBP was 165 and 96 mm Hg for subjects receiving HCTZ monotherapy; *P*<0.01, from baseline week 4 to the end of the first treatment period. At the end of the second treatment period, mean supine SBP and DBP was 154 and 86 mm Hg for subjects receiving combination treatment; from baseline week 4 to the end of the second treatment period; *P*<0.01 and *P*<0.001. At the end of the second treatment period, mean supine SBP and DBP was 155 and 90 mm Hg for subjects receiving HCTZ monotherapy; for both; *P*<0.001 from baseline week 4 to the end of the second treatment period. There were no statistically significant differences in blood pressure reduction between the 2 groups; *P* value not reported. Secondary: Not reported
Multicenter Diuretic Cooperative Study Group[34]	DB, MC, RCT Patients 21 to 69 years of age with mild to	N=179 12 weeks	Primary: Change from baseline in average supine SBP and	Primary: Baseline vs 12-week average supine blood pressure was 153/101 vs 139/93 mm Hg for amiloride, 160/100 vs 137/90 mm Hg for amiloride-HCTZ, and 154/101 vs 134/89 mm Hg for HCTZ. Reductions in supine blood pressure

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Amiloride 5 mg QD vs amiloride 5 mg and HCTZ 50 mg QD (combination entity) vs HCTZ 50 mg QD	moderate essential hypertension (supine DBP 95 to 115 mm Hg)		DBP Secondary: Heart rate, body weight, serum potassium	was significant in all treatment groups (*P*<0.01). The SBP reduction was greater with amiloride-HCTZ than with amiloride at all weeks and HCTZ at 4 and 8 weeks (*P*<0.05, both). Secondary: No significant changes from baseline in heart rate were observed with amiloride or HCTZ (*P* values not reported). An increase in heart rate was observed with amiloride-HCTZ of 3.3 bpm (*P*<0.05). Changes in body weight from baseline were –1.17 kg for amiloride-HCTZ, –0.72 kg for HCTZ, and 0.045 kg for amiloride (*P*<0.05, for amiloride-HCTZ only). Changes in serum potassium from baseline were 0.23 mEq/L for amiloride (*P*<0.01), –0.38 mEq/L for amiloride-HCTZ (*P*<0.01), and –0.59 mEq/L for HCTZ (*P*<0.01). The HCTZ change was statistically greater than the amiloride-HCTZ change (*P*<0.05). 23% of HCTZ, 2% of amiloride-HCTZ, and 0% of amiloride patients experienced hypokalemia.
Kohvakka, Eisalo, et al[35] Amiloride 5 mg QD in patients receiving HCTZ 50 mg QD (combination entity) vs triamterene 75 mg QD in patients receiving HCTZ 50 mg QD (combination entity) vs KCl 1,500 mg QD in patients receiving	PC, RCT, XO Patients 41 to 70 years of age with uncomplicated hypertension, previously treated with antihypertensive agents for 1 to 6 years	N=31 3 months	Primary: Changes in blood pressure, serum potassium, sodium, creatinine, urate, total body potassium Secondary: Not reported	Primary: No significant changes in blood pressure were observed with any of the treatment groups (*P* values not reported). Mean serum potassium was reduced in all active treatment groups except with the spironolactone group. KCl supplementation was least effective in elevating serum potassium. Total body potassium remained constant throughout treatment (*P* values not reported). Serum sodium remained within normal limits in all treatment groups (*P* values not reported). There were no significant changes in mean serum creatinine in any of the treatment groups (*P* values not reported). Serum urate concentration increased significantly in all treatment groups including HCTZ alone (*P* values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HCTZ 50 mg QD (separate entities) vs spironolactone 50 mg QD in patients receiving HCTZ 50 mg QD (separate entities) vs placebo				Not reported
Dean et al[36] Amiloride 5 mg QD and HCTZ 50 mg QD (combination entity) vs triamterene 50 mg QD and HCTZ 25 mg QD (combination entity)	RCT, SB, XO Patients with mild to moderate hypertension (DBP 95 to 110 mm Hg)	N=20 8 weeks	Primary: Blood pressure, hypokalemia, hyperkalemia, renal function tests Secondary: Not reported	Primary: The treatments produced a comparable effect on blood pressure. The baseline standing and lying blood pressure was 168/105 and 168/104 mm Hg, respectively. At week 8 of amiloride-HCTZ treatment, the standing and lying blood pressure was 145/92 and 145/90 mm Hg, respectively. At week 8 of triamterene-HCTZ treatment, the standing and lying blood pressure was 142/93 and 143/91 mm Hg, respectively (*P* values were not reported). There were no cases of hypokalemia or hyperkalemia and no renal function changes in either group (*P* values were not reported). Secondary: Not reported
Maxwell et al[37] Amiloride and HCTZ 1 tablet daily vs triamterene and HCTZ 1 capsule daily	OL, PRO, randomized Subjects with mild to moderate hypertension, mean supine DBP <90 mm Hg or >114 mm Hg at the end of the 3-week placebo phase	N=84 9 weeks	Primary: Mean blood pressure changes Secondary: Not reported	Primary: Of all subjects participating, 73% (30 subjects) of the triamterene-HCTZ group and 81% (35 subjects) of the amiloride-HCTZ group were maintained on one capsule or tablet daily throughout the study; no significant differences between treatment groups (*P* value not reported). At week 9, mean SBP and DBP was 136.2 and 87.4 mm Hg with triamterene-HCTZ (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All subjects received placebo for 3 weeks prior to the treatment phase. After 2 weeks of treatment, dosage could be increased to 2 capsules daily or 2 tablets daily.				At week 9, mean SBP and DBP was 132.6 and 85.7 mm Hg with amiloride-HCTZ (*P* value not reported). At week 9, mean serum potassium levels were 4.13 mEq/L with triamterene-HCTZ and 3.98 mEq/l with amiloride-HCTZ (*P* value <0.05 for the difference between the regimens). Secondary: Not reported
Williams et al[38] Phase 1 (Baseline, 2 weeks) Group 1: triamterene 37.5 mg-HCTZ 25 mg (Dyazide®), 2 capsules/day vs Group 2: triamterene 37.5 mg-HCTZ 25 mg (Dyazide®), 4 capsules/day vs Group 3: no antihypertensive medications Phase 2 (4 weeks) All groups: triamterene 75 mg-HCTZ 50 mg (Maxzide®) 1 tablet	3 phase, OL Patients 21 to 70 years of age, with essential hypertension, patients in 3 groups (Dyazide® 2 capsules/day, Dyazide® 4 capsules/day, or no antihypertensive treatment upon study entry)	N=156 (138 patients completed study) 6 to 32 weeks	Primary: Blood pressure and weight comparisons between phase 1 and phase 2 Secondary: Serum potassium concentrations	Primary: During phase 1, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking 2 Dyazide® capsules daily as prior therapy (Group 1) were: 91 mm Hg, 138 mm Hg, and 82 kg (*P* value not reported). During phase 2, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking 2 Dyazide® capsules daily as prior therapy (Group 1) were: 88 mm Hg, 135 mm Hg, and 82 kg (*P* value not reported). During phase 1, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking 4 Dyazide® capsules daily as prior therapy (Group 2) were: 93 mm Hg, 139 mm Hg, and 87 kg (*P* value not reported). During phase 2, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking 4 Dyazide® capsules daily as prior therapy (Group 2) were: 98 mm Hg, 149 mm Hg, and 79 kg (*P* value not reported). During phase 1, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking no prior therapy (Group 3) were: 98 mm Hg, 149 mm Hg, and 80 kg (*P* value not reported). During phase 2, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking no prior therapy (Group 3) were: 94 mm Hg, 136 mm Hg, and 78 kg (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily Phase 3 (up to 8 months) All groups: triamterene 75 mg-HCTZ 50 mg (Maxzide®) 1 tablet daily				Of these phase 1 and phase 2 comparisons, mean standing DBP and SBP differences were reported to be statistically significant during phase 2 for those subjects taking 2 Dyazide® capsules daily as prior therapy (Group 1; *P* value not reported) and for those subjects taking no prior therapy (Group 3; *P* value not reported). Additionally, the investigators concluded that patients with mild to moderate hypertensive who were taking 2 or 4 capsules of Dyazide® daily or no antihypertensive medications could be transferred safely to the combination of triamterene and HCTZ (Maxzide® 75/50 mg). Secondary: When patient taking Dyazide® 4 capsules/day were switched to Maxzide® 1 tablet daily, no patient became hypokalemic (serum potassium concentration <3.5 mEq/L) while taking the thiazide (*P* value not reported).

Drug regimen abbreviations: BID=twice daily, HCTZ=hydrochlorothiazide, KCl=potassium chloride, QD=once daily
Study abbreviations: DB=double-blind, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Other abbreviations: DBP=diastolic blood pressure, NYHA=New York Heart Association, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Combination Potassium-sparing Diuretics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
amiloride and hydrochlorothiazide	tablet	Moduretic®*	$	$
triamterene and hydrochlorothiazide	capsule, tablet	Dyazide®*, Maxzide®*	$	$

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

X. Conclusions

Clinical studies have demonstrated comparable efficacy between the amiloride and hydrochlorothiazide (HCTZ) combination and the triamterene and HCTZ combination in patients with hypertension and heart failure. The combinations have the same drug interactions, similar adverse events, comparable pharmacokinetics and are both administered once daily.[19-21]

The current heart failure and hypertension guidelines in this review do not recommend combination potassium-sparing diuretics as initial therapy, and many of these guidelines fail to mention these products as alternative agents or provide specific recommendations regarding the place in therapy of these products.[7-18] There are no studies that have demonstrated significant differences in clinical outcomes when the agents were administered separately as opposed to when they were taken as a combination product.[30-31] Combining angiotensin converting

enzyme inhibitors or angiotensin receptor blockers with potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high patients, leading to an additive or synergistic effect. As such, caution should be advised.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand combination potassium-sparing diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

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Pharmacotherapy Review of Thiazide Diuretics
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I. Overview

Diuretic agents have been widely used in the treatment of heart failure, hypertension, and various edematous conditions.[1] Diuretic therapy should generally be used in the treatment of hypertension, but more specifically, thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with agents from other classes.[2, 3-6] These agents are recommended for use in hypertensive patients, as well as in patients with current or previous symptoms of heart failure as well as those who exhibit evidence of fluid retention.[1] The thiazide diuretics are Food and Drug Administration (FDA)-approved for the management of edema as well as the management of hypertension.

The primary mechanism of action of the thiazide diuretics is an inhibition of the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride in approximately equivalent amounts. Additionally, common effects such as increased potassium and bicarbonate excretion, decreased calcium excretion, and uric acid retention may be observed. During initial thiazide therapy, a reduction in cardiac output and extracellular volume occurs. However, with chronic thiazide therapy, cardiac output normalizes and both peripheral vascular resistance and extracellular volume are reduced.[7]

When administered at their maximal therapeutic dosage, all agents of the thiazide diuretic class are approximately equal in both diuretic and/or natriuretic effects.[5] Generally, thiazide diuretic therapy is recommended at lower dosages for uncomplicated patients with mild to moderate hypertension and normal renal function. Higher doses of these agents are often required for patients who have resistant hypertension. Additionally, loop diuretics are the drugs of choice in patients with fluid overload due to heart failure or renal disease.[6]

The thiazide diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Thiazide Diuretics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
chlorothiazide	oral suspension, tablet	Diuril®*	Diuril®*, chlorothiazide
chlorothiazide sodium	injection	Diuril Sodium®	None
hydrochlorothiazide	capsule, tablet	Microzide®*	hydrochlorothiazide
methyclothiazide	tablet	Enduron®*†, Aquatensen®*†	methyclothiazide

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the thiazide diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of chronic heart failure and hypertension, please refer to the Appendix

Table 2. Treatment Guidelines Using the Thiazide Diuretics

Clinical Guideline	Recommendation(s)
American College of Cardiology (ACC)/American Heart	<u>Patients at Risk for Developing Heart Failure (Stage A)</u> • Systolic and diastolic hypertension should be controlled according to contemporary

Clinical Guideline	Recommendation(s)
Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[8]	guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • Diuretics are recommended to control pulmonary congestion and peripheral edema. Patients With Refractory End-Stage Heart Failure (Stage D) • Treatment of fluid retention is important.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[9]	Patients With Left Ventricular Systolic Dysfunction • An aldosterone antagonist may be added to the standard medication regimen (including diuretics) in patients who are in New York Heart Association (NYHA) functional class IV or those in class III previously in class IV (left ventricular ejection fraction ≤35%) from left ventricular systolic dysfunction. • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics are typically preferred. • Metolazone or chlorothiazide may be given to patients with persistent fluid retention despite high dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • Diuretics are recommended in patients with evidence of fluid overload. Patients With Acute Decompensated Heart Failure • Intravenous vasodilators, diuretics, and inotropes have all been used to treat patients with acute decompensated heart failure. Managing Patients With Heart Failure and Hypertension • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or calcium channel blocking agents (CCBs). • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)**[10]	• ACE inhibitors are recommended in patients with left ventricular ejection fraction 40%-45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention. • Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated. • A combination of digoxin and a β-blocker seems to be more efficacious to either agent alone in patients with atrial fibrillation. Digoxin may reduce hospitalizations in patients with heart failure caused by left ventricular systolic dysfunction and sinus rhythm who are already treated with ACE inhibitors, β-blockers, diuretics, and spironolactone (in severe heart failure).

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[2]	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[11]	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[12]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[13]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients. • Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment.
National Institute for	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic.

Clinical Guideline	Recommendation(s)
Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[14]	• If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes).
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[15]	• No specific recommendation is made concerning thiazide diuretics.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[16]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[17]	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[18]	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence.

III. Indications

Hydrochlorothiazide, chlorothiazide, and methyclothiazide have similar indications. These agents are indicated for various forms of edema and hypertension. More specifically, these agents are indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy; as well as in the management of hypertension, as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive medications in more severe hypertension. Additionally, these agents have been found useful in edema due to various forms of renal dysfunction including nephrotic syndrome, acute glomerulonephritis, and chronic renal failure

FDA-approved indications for the thiazide diuretics 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 Thiazide Diuretics[3-5,19-23]

Drug	Edema	Hypertension
Chlorothiazide	✔	✔
Chlorothiazide sodium*	✔	✔
Hydrochlorothiazide†	✔ †	✔
Methyclothiazide	✔	✔

* Diuril® sodium is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension. Diuril® sodium has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.
† Hydrochlorothiazide is indicated in the adjunctive treatment of edema. Microzide® is indicated in the management of hypertension either as the sole therapeutic agent, or in combination with other antihypertensives. Microzide® may be used in those patients in whom the development of hyperkalemia cannot be risked, including patients taking angiotensin converting enzyme inhibitors.

IV. Pharmacokinetics

The pharmacokinetic parameters for the thiazide diuretics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Thiazide Diuretics[3-5,19-23]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Chlorothiazide	Not reported	Not reported	Not metabolized	Not reported	10-15	Urine	45-120 minutes
Chlorothiazide sodium	Not reported	Not reported	Not appreciably metabolized	Not reported	96	Urine	45-120 minutes
Hydrochlorothiazide	50-75	40-68	Not appreciably metabolized	Not reported	>95	Urine	6-15
Methyclothiazide	Not reported	Not reported	Not reported	None	Not reported	Urine	Not reported

V. Drug Interactions

Significant drug interactions with the thiazide diuretics are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Thiazide Diuretics[7]

Drug(s)	Significance Level	Interaction	Mechanism
Thiazides (chlorothiazide,	1	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in

Drug(s)	Significance Level	Interaction	Mechanism
hydrochlorothiazide, methyclothiazide)			plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Through a synergistic effect, the concurrent administration of a thiazide and a loop diuretic may lead to profound diuresis and serious abnormalities. At therapy initiation, monitor for dehydration and electrolyte abnormalities. Titrate carefully in small or intermittent doses.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse reactions reported with the thiazide diuretics are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Thiazide Diuretics[,23]

Adverse Event	Chlorothiazide	Chlorothiazide sodium	Hydrochlorothiazide	Methyclothiazide
Cardiovascular				
Hypotension	✔	✔	1-10	1-10
Necrotizing angiitis	✔	✔	-	<1
Orthostatic hypotension	✔	✔	1-10	1-10
Central Nervous System				
Dizziness	✔	✔	-	-
Fever	✔	✔	-	-
Headache	✔	✔	-	-
Restlessness	✔	✔	-	-
Vertigo	✔	✔	-	-

Adverse Event	Chlorothiazide	Chlorothiazide sodium	Hydrochlorothiazide	Methyclothiazide
Dermatological				
Alopecia	✔	✔	<1	-
Cutaneous vasculitis	-	-	-	<1
Erythema multiforme	✔	✔	<1	<1
Exfoliative dermatitis	✔	✔	<1	-
Photosensitivity	✔	✔	1-10	1-10
Purpura	✔	✔	-	-
Rash	✔	✔	-	-
Stevens-Johnson syndrome	✔	✔	<1	<1
Toxic epidermal necrolysis	✔	✔	<1	-
Urticaria	✔	✔	-	-
Vasculitis	-	-	-	<1
Endocrine/Metabolic				
Cholesterol increased	✔	✔	-	-
Hepatic function impairment	-	-	<1	<1
Hypercalcemia	-	-	<1	<1
Hyperglycemia	✔	✔	-	-
Hyperuricemia	✔	✔	-	-
Hypochloremic alkalosis	✔	✔	-	-
Hypokalemia	✔	✔	1-10	1-10
Hypomagnesemia	✔	✔	-	-
Hyponatremia	✔	✔	-	-
Triglycerides increased	✔	✔	-	-
Gastrointestinal				
Abdominal cramping	✔	✔	-	-
Anorexia	✔	✔	1-10	1-10
Constipation	✔	✔	-	-
Diarrhea	✔	✔	-	-
Epigastric distress	-	-	1-10	1-10
Gastric irritation	✔	✔	-	-
Nausea	✔	✔	-	-
Pancreatitis	✔	✔	<1	<1
Sialadenitis	✔	✔	-	-
Vomiting	✔	✔	-	-
Genitourinary				
Impotence	✔	✔	-	-
Hematologic				
Agranulocytosis	✔	✔	<1	<1
Aplastic anemia	✔	✔	<1	<1
Hemolytic anemia	✔	✔	-	<1
Leukopenia	✔	✔	<1	<1
Thrombocytopenia	✔	✔	<1	<1
Hepatic				
Jaundice	✔	✔	-	-
Neuromuscular/Skeletal				
Muscle spasm	✔	✔	-	-
Paresthesia	✔	✔	-	-
Weakness	✔	✔	-	-
Ocular				
Blurred vision	✔	✔	-	-
Xanthopsia	✔	✔	-	-
Renal				

Adverse Event	Chlorothiazide	Chlorothiazide sodium	Hydrochlorothiazide	Methyclothiazide
Glycosuria	✔	-	-	-
Hematuria	-	✔	-	-
Interstitial nephritis	✔	✔	<1	-
Renal dysfunction	✔	✔	-	-
Renal failure	✔	✔	<1	-
Respiratory				
Pneumonitis	✔	✔	-	-
Pulmonary edema	✔	✔	-	-
Respiratory distress	✔	✔	<1	<1
Other				
Allergic myocarditis	-	-	<1	-
Allergic reactions	-	-	<1	-
Anaphylactic reactions	✔	✔	<1	-
Eosinophilic pneumonitis	-	-	<1	-
Systemic lupus erythematosus	✔	✔	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the thiazide diuretics are summarized in Table 7.

Table 7. Usual Dosing for the Thiazide Diuretics[3-7,19-23]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Chlorothiazide	Edema: 0.5 to 1.0 g (10 to 20 mL) once or twice daily, often administered on alternate days or on three to five days each week Hypertension: Initial, 0.5 or 1.0 g (10 to 20 mL) daily as a single or divided doses; maintenance, adjust according to blood pressure response; some patients may require up to 2.0 g (40 mL) a day in divided doses Microzide® is recommended to be taken as 1 capsule daily, whether as monotherapy or in combination; maximum, 50 mg as the total daily dose	For diuresis and control of hypertension: 10 to 20 mg/kg daily in a single or two divided doses Infants less than 6 months old may require doses up to 30 mg/kg daily in two divided doses Maximum, infants up to 2 years old is 375 mg daily, children 2 to 12 years old is 1 g daily Hypertension: 1 to 2 mg/kg daily in single or two divided doses Infants less than 6 months old may require doses up to 3 mg/kg daily in two divided doses Maximum, infants up to 2 years old is 37.5 mg daily, children 2 to 12 years old is 100 mg daily	Suspension, oral: 250 mg/5 mL Tablet: 250 mg 500 mg
Chlorothiazide sodium*	Edema: 0.5 to 1.0 g (10 to 20 mL) once or twice daily, often administered on alternate days or three to five days each week	Intravenous use in infants and children has been limited and is not generally recommended.	Injection, vial: 500 mg base/vial

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertension: Initial, 0.5 or 1.0 g (10 to 20 mL) daily as a single or as divided doses; maintenance, adjust according to blood pressure response, some patients may require up to 2.0 g (40 mL) daily in divided doses		
Hydrochlorothiazide	Edema; Adjunct: 25 to 100 mg daily in single or divided doses Hypertension: Initial, 12.5 to 25 mg once daily, titrate as needed; maintenance, 50 to 100 mg daily in single or divided doses	Edema; Adjunct: 1 to 2 mg/kg daily in a single or two divided doses Infants less than 6 months old may require doses up to 3 mg/kg daily in two divided doses Maximum, infants up to 2 years old is 37.5 mg daily, children 2 to 12 years old is 100 mg daily Hypertension: 1 to 2 mg/kg daily in single or two divided doses Infants less than 6 months old may require doses up to 3 mg/kg daily in two divided doses Maximum, infants up to 2 years old is 37.5 mg daily, children 2 to 12 years old is 100 mg daily	Capsule: 12.5 mg Tablet: 12.5 mg 25 mg 50 mg
Methyclothiazide	Edema: 2.5 to 10 mg once daily; maximum, 10 mg daily Hypertension: 2.5 to 5 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg

* Diuril Sodium® should be reserved for patients unable to take oral medication or for emergency situations.

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials Using the Thiazide Diuretics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Heart Failure/Edema				
Faris et al[24] One diuretic (loop diuretics [furosemide, bumetanide], thiazide diuretics [chlorothiazide], or potassium-sparing diuretics [amiloride, triamterene]) vs placebo or with open control or one diuretic (loop diuretics [furosemide, bumetanide], thiazide diuretics [chlorothiazide], or potassium-sparing diuretics [amiloride, triamterene]) vs another active agent (eg, angiotensin converting enzyme inhibitors, digoxin)	MA 14 double-blinded, randomized control trials of diuretic therapy comparing loop, thiazide, or potassium-sparing diuretics with placebo or with open control; or one diuretic with another active agent in adult patients with chronic heart failure	N=525 2 to 52 weeks	Primary: Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Primary: Mortality was reported in 3 of the 7 placebo-controlled trials, and this analysis showed that mortality was lower for patients treated with diuretics than with placebo (3/111[2.7%] vs 12/110 [10.9%], respectively; OR, 0.24; 95% CI, 0.07 to 0.83; *P*=0.02). These results showed that patients treated with diuretics had an absolute risk reduction of 8% when compared to placebo and a number needed to treat of 12.5. Secondary: An analysis of pooled data from 2 trials showed lower admission rates for worsening heart failure in patients taking diuretics than in patients taking placebo (OR, 0.07; 95% CI, 0.01 to 0.52; *P*=0.01). Diuretics were found to improve exercise capacity, with a difference in means of 0.74 (95% CI, 0.37 to 1.11; *P*<0.0001) and of 0.67 (95% CI, 0.02 to 1.31; *P*=0.04.), respectively. The combined results of these 4 trials indicated that diuretics improved exercise capacity in participants with chronic heart failure with a difference in means of 0.72 (95% CI, 0.40 to 1.04; *P*<0.0001).
Rengo et al[25]	RCT	N=30	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HCTZ 150 mg QD vs amiloride 15 mg QD vs amiloride 15 mg QD and HCTZ 150 mg QD (combination entity)	Patients 35 to 60 years of age with liver cirrhosis and ascites or congestive heart failure	15 days	Body weight, 24 hour diuresis, serum sodium, serum potassium, sodium and potassium urinary loss Secondary: Not reported	All groups had a statistically significant reduction in body weight from baseline (*P*<0.001, all groups). Combination amiloride-HCTZ showed a significantly greater reduction compared to amiloride alone (*P*<0.001). All groups significantly differed from baseline in 24 hour diuresis (*P*<0.01). Amiloride-HCTZ and HCTZ resulted in more diuresis than amiloride (*P*<0.001, for both). Serum sodium was reduced from baseline in all groups. HCTZ alone had a significantly greater reduction than amiloride (*P*<0.01), and amiloride-HCTZ (*P*<0.001). Sodium urinary loss was seen in all treatments at day 2, amiloride-HCTZ had maintained this loss at day 5 (*P*<0.001, for both). Serum potassium decreased in the HCTZ group but increased in the amiloride and amiloride-HCTZ groups. HCTZ alone resulted in a marked increase in potassium urinary loss (*P*<0.001). Secondary: Not reported
Kohvakka[26] HCTZ 50 mg BID vs amiloride 5 mg BID in patients receiving HCTZ 50 mg BID (combination entity) vs triamterene 75 mg BID in patients receiving HCTZ 50 mg BID (combination entity)	RCT, XO Patients 41 to 69 years of age with congestive heart failure(NYHA class II-III), average cardiac failure duration of 9.3 years, average previous diuretic treatment duration of 6.8 years, developed persistent hypokalemia on HCTZ alone	N=25 5 months	Primary: Changes in weight, blood pressure, serum sodium, serum potassium, total body potassium Secondary: Percentage with hypokalemia, median days until hypokalemia detection, serum magnesium	Primary: Weight loss was statistically significant in the amiloride-HCTZ and triamterene-HCTZ groups (*P*=0.05, both groups) but not in the KCl-HCTZ group (*P* value not reported) compared to HCTZ alone. No statistically significant changes in blood pressure were observed (*P* values not reported). No statistically significant differences in serum sodium were observed in the amiloride-HCTZ or triamterene-HCTZ groups (*P* values not reported). Serum sodium was slightly higher in the KCl-HCTZ group compared to HCTZ alone (*P*=0.01). Serum potassium was found to be significantly higher in all treatment groups compared to HCTZ alone (*P*=0.01, for all groups). Total body potassium was significantly higher with amiloride-HCTZ and triamterene-HCTZ (*P*=0.05, both groups) but not with KCl-HCTZ (*P* value not reported) compared to HCTZ alone.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs KCl 1 g BID in patients receiving HCTZ 50 mg BID (separate entities)				Secondary: The percentages of patients that became hypokalemic were 39% in the amiloride-HCTZ group, 52% in the triamterene-HCTZ group, and 52% in KCl-HCTZ group (*P* values not reported). The median days until hypokalemia detection were 114 for amiloride-HCTZ, 75 for triamterene-HCTZ, and 51.5 for KCl-HCTZ (*P* values not reported). Serum magnesium was maintained at a statistically higher rate with amiloride-HCTZ and triamterene-HCTZ than with KCl-HCTZ (*P* values not reported).
Cheitlin et al[27] Amiloride 5 or 10 mg QD for 7 days, placebo QD for the next 14 days, along with HCTZ 50 or 100 mg QD (separate entities) vs placebo QD for 14 days, amiloride 5 or 10 mg QD for the next 7 days, along with HCTZ 50 or 100 mg QD (separate entities)	DB, PC, RCT, XO Patients with an average age of 63 and a history of congestive heart failure and ≥1 episode of pulmonary edema (NYHA class II-III) who were not previously treated	N=11 21 days	Primary: Hemodynamic changes at rest and exercise Secondary: Not reported	Primary: At rest, there were no significant differences between patients treated with placebo or amiloride in right atrial pressure, pulmonary atrial pressure, heart rate, pulmonary artery wedge pressure, systemic arterial pressure, right ventricular stroke work index, left ventricular stroke work index, systemic vascular resistance, cardiac index, or stroke volume index (*P* values not reported). During exercise, there were significant differences between patients treated with placebo or amiloride at the 50-watt stage in right atrial pressure (15.0 vs 10.5 mm Hg), pulmonary artery wedge pressure (28.6 vs 22.1 mm Hg), pulmonary artery diastolic pressure (32.2 vs 21.6 mm Hg), mean pulmonary artery pressure (44.4 vs 38.9 mm Hg), left ventricular stroke work index (69.5 vs 77.9 g-m/m^2), and stroke volume index (44.9 vs 46.2 cc/beat/m^2), respectively (*P* values not reported). There were no significant differences between placebo and amiloride during exercise in right ventricular stroke work index, heart rate, aortic pressure, cardiac index, and total systemic vascular resistance (*P* values not reported). Secondary: Not reported
Hypertension				
Baguet et al[28]	MA	N=10,818	Primary: Weighted average	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Antihypertensive drugs considered for inclusion were HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, candesartan cilexetil*, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan, and aliskiren Although the diuretics cicletanine*, furosemide, and spironolactone were considered for inclusion, none of the studies relating to these agents satisfied all inclusion criteria.	80 randomized, double-blind trials where the drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages including patients aged >18 years with mild or moderate essential hypertension (SBP blood pressure 140–179 mm Hg and/or DBP 90–109 mm Hg)	8 to 12 weeks	reductions in SBP and DBP Secondary: Not reported	or formal comparisons between drugs. Diuretics (–19.2 mm Hg; 95% CI, –20.3 to –18.0), calcium channel blockers (–16.4 mm Hg; 95% CI, –17.0 to –15.8) and angiotensin converting enzyme inhibitors (–15.6 mm Hg; 95% CI, –17.6 to –13.6) produced the greatest reductions in SBP from baseline (*P* values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (–11.4 mm Hg; 95% CI, –12.0 to –10.9), calcium channel blockers (–11.4 mm Hg; 95% CI, –11.8 to –11.1), and diuretics (–11.1 mm Hg; 95% CI, –11.7 to –10.5). *P* values were not reported. The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: –19.2 mm Hg (95% CI, –20.3 to –18.0) and –11.1 mm Hg (95% CI, –11.7 to –10.5), respectively. β-Blockers: –14.8 mm Hg (95% CI, –15.9 to –13.7) and –11.4 mm Hg (95% CI, –12.0 to –10.9), respectively. Calcium channel blockers: –16.4 mm Hg (95% CI, –17.0 to –15.8) and –11.4 mm Hg (95% CI, –11.8 to –11.1), respectively. Angiotensin converting enzyme inhibitors: –15.6 mm Hg (95% CI, –17.6 to –13.6) and –10.8 mm Hg (95% CI, –11.9 to –9.7), respectively. Angiotensin II receptor antagonists: –13.2 mm Hg (95% CI, –13.6 to –12.9) and –10.3 mm Hg (95% CI, –10.5 to –10.1), respectively. Renin inhibitor: –13.5 mm Hg (95% CI, –14.2 to –12.9) and –11.3 mm Hg (95% CI, –11.7 to –10.9), respectively. *P* values not reported. Secondary: Not reported
Valmin K et al[29] HCTZ 12.5 mg BID vs furosemide 12.5, 25, or 40 mg BID	DB, RCT, XO, 5 experimental periods each of 4 weeks Men and women with essential hypertension	N=34 20 weeks	Primary: Blood pressure, urinary output, serum electrolytes, safety and tolerability Secondary: Not reported	Primary: When compared to placebo, there was a significant reduction of blood pressure with HCTZ 12.5 mg twice daily and furosemide 12.5 mg twice daily ($P<0.05$). Paired comparison showed that HCTZ 12.5 mg twice daily and furosemide 25 and 40 mg twice daily had a similar hypotensive effect, irrespective of the initial blood pressure ($P>0.10$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				When compared to placebo, the urinary output increased significantly with furosemide 12.5, 25, or 40 mg twice daily ($P<0.05$, $P<0.01$ and $P<0.001$, respectively) but not with the HCTZ group ($P>0.10$). Sodium level did not alter during the various treatment periods when compared with the placebo period, or between the individual treatment periods ($P>0.10$). Potassium level fell significantly during the HCTZ period ($P<0.001$) and furosemide 25 and 40 mg twice daily period ($P<0.01$ and $P<0.001$, respectively). Potassium level was not significantly affected with furosemide 12.5 mg twice daily ($P>0.10$). Side effects including headache, dizziness, fatigue and nausea were more marked during the run-in period and placebo periods compared to the active treatment with high doses of drugs (*P* value not reported). Secondary: Not reported
Hua et al[30] Chlorothiazide 0 to 5 g BID vs metolazone 5 mg QD	XO Patients with hypertension	N=20 Duration not specified	Primary: Blood pressure, serum potassium Secondary: Not reported	Primary: Blood pressures on metolazone tended to be lower than on chlorothiazide, but the difference was not statistically significant (*P* values not reported). Both agents significantly lowered serum potassium concentrations and total body potassium to a similar degree. However, the serum potassium did not fall below the normal range in any patient and no potassium supplements were required (*P* values not reported). Secondary: Not reported
Carter et al[31] Chlorthalidone 12.5 to 600 mg/day vs HCTZ 12.5 to 450 mg/day	MA Included studies which evaluate the pharmacokinetic and blood pressure lowering effects of chlorthalidone and HCTZ	N=200 Duration varied per study	Primary: Blood pressure Secondary: Serum potassium	Primary: In a dose equivalence study comparing HCTZ 100 mg QD to chlorthalidone 50 mg QD, blood pressure (SBP/DBP) reduced by 18/8 and 25/10 mm Hg compared to baseline, respectively (*P* value not reported). In another study comparing HCTZ 25 mg and triamterene 50 mg QD, HCTZ 50 mg and triamterene 100 mg QD, and chlorthalidone 50 mg QD, the blood pressure reduction was 15/8, 18/12, and 25/16 mm Hg, respectively (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				One other dose equivalence study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, blood pressure reduction was 22/16 and 18/15 mm Hg, respectively (*P* values not reported). All available studies were inspected and it was concluded that HCTZ 50 mg is approximately equivalent to chlorthalidone 25 to 37 mg. Furthermore, it was suggested that chlorthalidone doses should generally be approximately 50% to 75% of the typical HCTZ dose. Secondary: In a study comparing HCTZ 100 mg QD and chlorthalidone 50 mg QD, potassium increased slightly with chlorthalidone (0.02 mEq/L) and decreased significantly with HCTZ (0.22 mEq/L; *P*=0.009). However, in another study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, serum potassium decreased by 0.38 mEq/L with HCTZ and by 0.03 mEq/L with chlorthalidone. The difference was not statistically significant (*P*<0.07).
Ernst et al[32] HCTZ 25 mg QAM vs chlorthalidone 12.5 mg QAM At week 4, both HCTZ and chlorthalidone were titrated to 50 mg QAM and 25 mg QAM, respectively for the remainder of the study.	Active-treatment, RCT, SB, XO Men and women aged 18 to 79 years with prehypertension or a new or established diagnosis of hypertension (stage 1 or 2), not receiving antihypertensive medications, and had an average office blood pressure value in the last 6 months between 140 and	N=30 8 weeks plus 4 week washout period	Primary: Comparison of the change in 24-hour mean SBP and DBP from baseline to week 8 Secondary: Comparison of changes in mean SBP and mean DBP for office blood pressure at each visit, change in ambulatory daytime and nighttime mean SBP and DBP from baseline to week 8, development of hypokalemia (defined	Primary: At week 8, there was a greater reduction in 24-hour mean SBP with chlorthalidone 25 mg/day compared to HCTZ 50 mg/day compared to baseline (−12.4±1.8 vs −7.4±1.7 mm Hg, respectively; *P*=0.054). Secondary: There was a trend in favor of greater reduction in SBP with chlorthalidone than with HCTZ at each office visit. However, the difference was only statistically significant at week 2 (−15.7±2.2 vs −4.5±2.1 mm Hg, respectively; *P*=0.001). Although mean reductions in DBP was also greater with chlorthalidone compared to HCTZ at each study visit, the differences were not statistically significant at any visit (*P*>0.89 for all). The reduction in SBP during nighttime hours was −13.5±1.9 mm Hg for chlorthalidone and −6.4±1.7 mm Hg for HCTZ (*P*=0.009). The reduction in daytime mean SBP between both groups was not significantly different (−11.4±2.0 vs −8.1±1.9 mm Hg, respectively; *P*=0.230).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	179 mm Hg systolic or 90 and 109 mm Hg diastolic		as serum potassium <3.5 mEq/L	Changes in serum potassium were similar between treatment groups (*P*=0.76). The incidence of hypokalemia was 50% in patients taking HCTZ and 46% in patients taking chlorthalidone (*P*=0.682).
Araoye et al[33] HCTZ 50 mg BID vs furosemide 40 mg BID	DB, XO Patients with hypertension	N=not specified 3 months	Primary: Blood Pressure Secondary: Not reported	Primary: Furosemide and HCTZ significantly reduced blood pressure (*P* value not reported). The decrease in blood pressure was consistently greater in the HCTZ group than with furosemide (*P* value not reported); however the difference was significant in regards to SBP only (*P* value not reported). Secondary: Not reported
Madkour et al[34] HCTZ 50 mg QD vs indapamide 2.5 mg QD	RCT Patients aged 32 to 70 years with impaired renal function for 1 to 15 years and moderate hypertension for 2 to 27 years, initial creatinine clearance between 32 and 80 mL/min/1.73 m^2 body surface area	N=28 24 months	Primary: Blood pressure, changes in creatinine clearance Secondary: Not reported	Primary: Blood pressure normalized in all patients taking either indapamide or HCTZ. There were no significant differences in SBP or DBP between groups (*P* value not reported). At 24 months, creatinine clearance progressively increased from 58±4.4 to 72±4.4 mL/min/1.73 m^2 body surface area in patients treated with indapamide (*P*<0.01). However, creatinine clearance progressively decreased from 65±3.0 to 53±3.0 mL/min/1.73 m^2 body surface area in patients treated with HCTZ (*P*<0.01). Therefore, creatinine clearance significantly increased by 28.5±4.4% with indapamide and decreased by 17.4±3.0% with thiazide therapy (*P*<0.01). Secondary: Not reported
Ames[35] ≤ 25 mg of HCTZ or its equivalent in other thiazides, up to 112.5 mg QD vs	MA 13 clinical trials evaluating the effects of thiazides and indapamide on blood lipids and blood pressure as monotherapy for	N=1,547 1 to 25 months	Primary: Comparison of the effects of thiazides and indapamide on blood lipids and blood pressure Secondary: Not reported	Primary: The mean change from baseline was 1.4% for total cholesterol, 5.5% for high density lipoprotein cholesterol, and ─0.5% for triglycerides with indapamide. None of the differences were statistically significant (*P* value not reported). Low-dose thiazide therapy did not decrease total cholesterol at any data point. The mean percent increase in total cholesterol was 3.8%, in high density lipoprotein cholesterol was 3.1%, and in triglycerides was 10.8%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
indapamide 2.5 mg QD HCTZ was the most commonly studied thiazide; therefore, all other thiazides were expressed as approximate mg equivalents of HCTZ.	hypertension			with low-dose HCTZ. The increases in total cholesterol and triglycerides from baseline was statistically significant (*P*<0.01). The mean change in total cholesterol was 6.3%, in high density lipoprotein cholesterol was ─0.5%, and in triglycerides was 19.5% for higher doses of HCTZ. Increases from baseline in total cholesterol and triglycerides were statistically significant (*P* value not reported). SBP decreased more with higher doses of HCTZ than with low-dose thiazide therapy (*P*<0.05). The effects of indapamide on systolic arterial pressure were intermediate between, and not statistically different from, either thiazide dose. Decreases in DBP did not differ among groups (*P* value not reported). Secondary: Not reported
Larochelle et al[36] HCTZ 50 mg vs HCTZ 50 mg and amiloride 5 mg	DB, RCT Ambulant patients, 18 to 70 years of age with essential hypertension who after not being treated for at least 2 weeks prior to the study had a supine DBP of 95 to 109 mm Hg and a serum potassium level of >3.5 mmol/L	N=266 8 weeks	Primary: Blood pressure and serum potassium concentration Secondary: Not reported	Primary: At 8 weeks, there were no statistically significant differences between groups in the mean blood pressure reductions (*P* value not reported). During the 8 weeks of treatment, the group receiving combination therapy experienced a decrease in the mean supine blood pressure and mean serum potassium level. Respectively these reductions were from 156/99 to 138/88 mm Hg and from 4.23 to 3.91 mmol/L. During the 8 weeks of treatment, the monotherapy group experienced a reduction in the mean supine blood pressure and mean serum potassium level; respectively from 157/99 to 138/87 mm Hg and from 4.16 to 3.69 mmol/L. Hypokalemia occurred less frequently in the combination group than in the monotherapy group (respectively, 14% and 29%; *P*=0.0026). However, the proportions of patients with a potassium level exceeding 4.5 mmol/L were similar 4.5% and 3.9%, respectively (*P* value not reported). Secondary: Not reported
Salmela et al[37]	DB, MC, PG, RCT	N=40	Primary: Changes in blood	Primary: At the end of the first treatment period, mean supine SBP and DBP was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HCTZ 25 mg daily vs amiloride 2.5 mg plus HCTZ 25 mg daily	Men and women with mild to moderate hypertension, mean 66.7 years of age	12 weeks	pressure Secondary: Not reported	161 and 91 mm Hg for subjects receiving combination treatment; from baseline week 4; *P*<0.01 and *P*<0.001, respectively. At the end of the first treatment period, mean supine SBP and DBP was 165 and 96 mm Hg for subjects receiving HCTZ monotherapy; *P*<0.01, from baseline week 4 to the end of the first treatment period. At the end of the second treatment period, mean supine SBP and DBP was 154 and 86 mm Hg for subjects receiving combination treatment; from baseline week 4 to the end of the second treatment period; *P*<0.01 and *P*<0.001. At the end of the second treatment period, mean supine SBP and DBP was 155 and 90 mm Hg for subjects receiving HCTZ monotherapy; for both; *P*<0.001 from baseline week 4 to the end of the second treatment period. There were no statistically significant differences in blood pressure reduction between the 2 groups; *P* value not reported. Secondary: Not reported
Multicenter Diuretic Cooperative Study Group[38] HCTZ 50 mg QD vs amiloride 5 mg and HCTZ 50 mg QD (combination entity) vs amiloride 5 mg QD	DB, MC, RCT Patients 21 to 69 years of age with mild to moderate essential hypertension (supine DBP 95 to 115 mm Hg)	N=179 12 weeks	Primary: Change from baseline in average supine SBP and DBP Secondary: Heart rate, body weight, serum potassium	Primary: Baseline vs 12-week average supine blood pressure was 153/101 vs 139/93 mm Hg for amiloride, 160/100 vs 137/90 mm Hg for amiloride-HCTZ, and 154/101 vs 134/89 mm Hg for HCTZ. Reductions in supine blood pressure was significant in all treatment groups (*P*<0.01). The SBP reduction was greater with amiloride-HCTZ than with amiloride at all weeks and HCTZ at 4 and 8 weeks (*P*<0.05, both). Secondary: No significant changes from baseline in heart rate were observed with amiloride or HCTZ (*P* values not reported). An increase in heart rate was observed with amiloride-HCTZ of 3.3 bpm (*P*<0.05). Changes in body weight from baseline were –1.17 kg for amiloride-HCTZ, –0.72 kg for HCTZ, and 0.045 kg for amiloride (*P*<0.05, for amiloride-HCTZ only). Changes in serum potassium from baseline were 0.23 mEq/L for amiloride

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*P*<0.01), –0.38 mEq/L for amiloride-HCTZ (*P*<0.01), and –0.59 mEq/L for HCTZ (*P*<0.01). The HCTZ change was statistically greater than the amiloride-HCTZ change (*P*<0.05). 23% of HCTZ, 2% of amiloride-HCTZ, and 0% of amiloride patients experienced hypokalemia.
Kohvakka, Eisalo, et al[39] Amiloride 5 mg QD in patients receiving HCTZ 50 mg QD (combination entity) vs triamterene 75 mg QD in patients receiving HCTZ 50 mg QD (combination entity) vs KCl 1,500 mg QD in patients receiving HCTZ 50 mg QD (separate entities) vs spironolactone 50 mg QD in patients receiving HCTZ 50 mg QD (separate entities) vs placebo	PC, RCT, XO Patients 41 to 70 years of age with uncomplicated hypertension, previously treated with antihypertensive agents for 1 to 6 years	N=31 3 months	Primary: Changes in blood pressure, serum potassium, sodium, creatinine, urate, total body potassium Secondary: Not reported	Primary: No significant changes in blood pressure were observed with any of the treatment groups (*P* values not reported). Mean serum potassium was reduced in all active treatment groups except with the spironolactone group. KCl supplementation was least effective in elevating serum potassium. Total body potassium remained constant throughout treatment (*P* values not reported). Serum sodium remained within normal limits in all treatment groups (*P* values not reported). There were no significant changes in mean serum creatinine in any of the treatment groups (*P* values not reported). Serum urate concentration increased significantly in all treatment groups including HCTZ alone (*P* values not reported). Secondary: Not reported

*Agent not available in the United States (US)
Drug regimen abbreviations: BID=twice daily, KCL=potassium chloride, QAM=every morning, QD=once daily,
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single blind, SR=sustained release, XO=crossover
Other abbreviations: β-blockers=β-adrenergic blocking agents, bpm=beats per minute, CCBs=calcium channel blocking agents, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, NYHA=New York Heat Association, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Thiazide Diuretics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
chlorothiazide	oral suspension, tablet	Diuril®*	$	$
chlorothiazide sodium	injection	Diuril Sodium®	$$$$$	N/A
hydrochlorothiazide	capsule, tablet	Microzide®*	$$$	$
methyclothiazide	tablet	Enduron®*†, Aquatensen®*†	N/A	$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

All single entity agents within the thiazide class are Food and Drug Administration (FDA) approved for the treatment of hypertension and edema.[3-5, 19-23] No head-to-head clinical trials comparing the efficacy of the thiazide diuretic agents to each other for their FDA approved indications were identified.

For the treatment of edema related to congestive heart failure, the American College of Cardiology/American Heart Association (ACC/AHA) recommends diuretics. Diuretics and salt restriction are indicated in patients with current or previous symptoms of heart failure and evidence of fluid retention due to reduced left ventricular ejection fraction. A thiazide-type diuretic, including both thiazide and thiazide-like diuretics, may be preferred in

hypertensive heart failure patients with mild fluid retention as a result of more persistent antihypertensive effects.[8] Diuretics are also recommended in patients with heart failure and normal left ventricular ejection fraction to control pulmonary congestion and peripheral edema. Similar recommendations are made from the Heart Failure Society of America (HFSA).[9]

For the treatment of hypertension, the major national guidelines including the Seventh Report of the Joint National Committee (JNC 7), all recommend a diuretic agent to be considered as initial therapy.[2, 11, 13-14] Additionally, the JNC 7 guidelines and the Medical letter recommend a thiazide-type diuretic, including both thiazide and thiazide-like diuretics, to be the initial therapy in many patients with uncomplicated hypertension as monotherapy or in combination with other antihypertensive agents.[2, 13] The National Institute for Health and Clinical Excellence (NICE), guidelines also recommend thiazide type diuretics first-line, but only in those aged 55 years or older.[14] Guidelines do not designate one thiazide diuretic as preferred over the others.

With the exception of chlorothiazide sodium all agents in this class are available generically in at least one dosage form. Since guidelines do not designate one thiazide diuretic for general use over another, the use of chlorothiazide sodium, an intravenous product, should be reserved for adult patients who are unable to take oral medications or are experiencing an emergency situation.[5, 20, 23] Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand thiazide diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine 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 Thiazide-like Diuretics
AHFS Class 402824
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I. Overview

Diuretic agents have been widely used in the treatment of heart failure, hypertension, and various edematous conditions. Diuretics are recommended in patients with current or previous symptoms of heart failure as well as those who exhibit evidence of fluid retention.[1] Thiazide diuretics, including thiazide-like diuretics, may be preferred in hypertensive heart failure patients with mild fluid retention compared to other classes of diuretics.[1] Diuretics in general should be used in the treatment of hypertension, but more specifically, thiazide-type diuretics, including both thiazide and thiazide-like diuretics, should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with agents from other classes.[2]

Thiazide-like diuretics are Food and Drug Administration (FDA)-approved for the management of edema associated with congestive heart failure or other conditions as well as the management of hypertension either as monotherapy or in combination with other antihypertensive agents.[3-9] Thiazide-like diuretics exhibit mechanisms of action similar to those of the thiazide diuretics. Their primary mechanism of action is inhibition of sodium reabsorption in the distal convoluted tubule of the nephron.[3] This results in an initial modest reduction in plasma volume and cardiac output.[10] However, long-term maintenance of decreased blood pressure has been shown to be associated with partial reversal of the hemodynamic changes as plasma volume and cardiac output return towards the baseline level.[10] Although thiazide-like diuretics are pharmacologically similar to thiazide diuretics, there are chemical differences in the molecular structure, such as the incorporation of a double ring system or a methylindoline ring system, that differentiate thiazide-like from thiazide diurectics.[5,11] In addition, indapamide may also produce an independent vascular action which results in a reduction in total peripheral resistance.[9] Also, metolazone does not significantly decrease the renal plasma flow and may produce diuresis in patients with glomerular filtration rates <20 mL/minute.[11] All agents are available generically in tablet form. Chlorthalidone has also been formulated with povidone polyvinylpyrrolidone (PVP) to enhance bioavailability and this formulation, available as a 15 mg tablet is not currently available generically.

The thiazide-like diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Thiazide-like Diuretics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
chlorthalidone	tablet	Hygroton*†, Thalitone	chlorthalidone
indapamide	tablet	Lozol®*†	indapamide
metolazone	tablet	Zaroxolyn®*	metolazone

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the thiazide-like diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of heart failure and hypertension, please refer to the Appendix

Table 2. Treatment Guidelines Using the Thiazide-like Diuretics

Clinical Guideline	Recommendation(s)
American College of	Patients at Risk for Developing Heart Failure (Stage A)

Clinical Guideline	Recommendation(s)
Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[1]	• Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • Diuretics are recommended to control pulmonary congestion and peripheral edema. Patients With Refractory End-Stage Heart Failure (Stage D) • Treatment of fluid retention is important.
Heart Failure Society of America (HFSA): **2006 Comprehensive Heart Failure Practice Guideline (2006)**[12]	Patients With Left Ventricular Systolic Dysfunction • An aldosterone antagonist may be added to the standard medication regimen (including diuretics) in patients who are in New York Heart Association (NYHA) functional class IV or those in class III previously in class IV (left ventricular ejection fraction ≤35%) from left ventricular systolic dysfunction. • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics are typically preferred. • Metolazone or chlorothiazide may be given to patients with persistent fluid retention despite high dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • Diuretics are recommended in patients with evidence of fluid overload. Patients With Acute Decompensated Heart Failure • Intravenous vasodilators, diuretics, and inotropes have all been used to treat patients with acute decompensated heart failure. Managing Patients With Heart Failure and Hypertension • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or calcium channel blocking agents (CCBs). • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)**[13]	• ACE inhibitors are recommended in patients with left ventricular ejection fraction 40%-45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention. • Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated. • A combination of digoxin and a β-blocker seems to be more efficacious to either agent alone in patients with atrial fibrillation. Digoxin may reduce hospitalizations in patients with heart failure caused by left ventricular systolic dysfunction and sinus rhythm who are already treated with ACE inhibitors, β-blockers, diuretics, and

Clinical Guideline	Recommendation(s)
	spironolactone (in severe heart failure).
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7) (2004)**[2]	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension (2003)**[14]	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension (EHS)/European Society of Cardiology (ESC): **2007 Guidelines for the Management of Hypertension (2007)**[15]	• There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Drugs for Hypertension (2005)**[16]	• Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients.

Clinical Guideline	Recommendation(s)
	• Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)**[17]	• Initial therapy in patients ≥55 years of age should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes).
British Hypertension Society (BHS): **Guidelines for Hypertension Management 2004 (BHS-IV)**[18]	• No specific recommendation is made concerning thiazide-like diuretics.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[19]	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans (2003)**[20]	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[21]	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-

Clinical Guideline	Recommendation(s)
	acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence.

III. Indications

FDA-approved indications for the thiazide-like diuretics 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 Thiazide-like Diuretics[3-4,6-8]

Indication	Chlorthalidone	Indapamide	Metolazone
Hypertension			
Management of hypertension either as the sole therapeutic agent or to enhance the effect of other antihypertensive drugs	✔ *		
For the treatment of hypertension, alone or in combination with other antihypertensive drugs		✔	✔ †
Edema			
Edema associated with congestive heart failure	✔ ‡		
Salt and fluid retention associated with congestive heart failure		✔	
Salt and water retention, including edema accompanying congestive heart failure			✔
Edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure	✔		
Salt and water retention, including edema accompanying renal disease, including the nephrotic syndrome and states of diminished renal function			✔
Edema associated with hepatic cirrhosis	✔ ‡		
Edema associated with corticosteroid and estrogen therapy	✔ ‡		

*Product information for generic chlorthalidone tablets specifies that combination therapy is indicated in the more severe forms of hypertension.
†Alone or in combination with other antihypertensive drugs of a different class.
‡As adjunctive therapy.

IV. Pharmacokinetics

The pharmacokinetic parameters for the thiazide-like diuretics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Thiazide-like Diuretics[3-9]

Drug	Bio-availability (%)	Protein Binding (%)	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Chlorthalidone	65 104-116 (with PVP)	75	None	50-74	Not reported	40-89
Indapamide	~100	71-79	Not reported	60-70	Renal (60-70%), Gastrointestinal tract (23%), Feces (16-20%)	14-15
Metolazone	40-65	95	Not reported	56.1	Renal (56.1%)	8-14

PVP=povidone polyvinylpyrrolidone.

V. Drug Interactions

Significant drug interactions with the thiazide-like diuretics are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Thiazide-like Diuretics[3]

Drug(s)	Significance Level	Interaction	Mechanism
Thiazide-like diuretics (all)	1	Cisapride	Cisapride may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes. Cisapride is contraindicated in patients who may experience a rapid reduction in plasma potassium, such as those receiving thiazide diuretics.
Thiazide-like diuretics (all)	1	Digitalis glycosides (digitoxin, digoxin)	Thiazide-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium; supplement low levels. Prevent further losses with dietary sodium restriction or potassium-sparing diuretics.
Thiazide-like diuretics (all)	1	Dofetilide	Hypokalemia may occur, increasing the risk of torsades de pointes. Coadministration of dofetilide and thiazide diuretics, alone and in combination with potassium-sparing diuretics such as triamterene, is contraindicated.
Thiazide-like diuretics (all)	2	Diazoxide	Hyperglycemia, often with symptoms similar to frank diabetes, may occur. The effect appears to return to pretreatment values ~2 weeks after these medications are discontinued. Decreased dosage of 1 or both agents may be required. Frequent monitoring of blood and urine glucose levels is essential. Avoid this combination if possible.
Thiazide-like diuretics (all)	2	Lithium	Thiazide diuretics increase serum lithium levels. Monitor plasma lithium levels and observe the patient for symptoms of toxicity. Adjust dose accordingly.
Thiazide-like diuretics (all)	2	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Both groups have synergistic effects that may result in profound diuresis and serious electrolyte abnormalities. Carefully titrate with small or intermittent doses. Monitor for dehydration and electrolyte abnormalities at the start of combined therapy.
Thiazide-like diuretics (all)	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Thiazide diuretics increase fasting blood glucose and may decrease sulfonylurea hypoglycemia. This effect may occur after several days to many months of thiazide therapy. Hyponatremia also may occur. Closely monitor blood glucose. If hyperglycemia develops, possibly increase the sulfonylurea dose.

Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse reactions reported with the thiazide-like diuretics are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Thiazide-like Diuretics[3-9]

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Cardiovascular			
Chest pain	-	<5	✔
Hemoconcentration	-	-	✔
Irregular heartbeat	-	<5	-
Orthostatic hypotension	✔	<5	✔
Palpitations	-	<5	✔
Premature ventricular contractions	-	<5	-
Venous thrombosis	-	-	✔
Volume depletion	-	-	✔
Central Nervous System			

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Anxiety	-	≥5	-
Blurred vision	-	<5	✔
Depression	-	<5	-
Dizziness	✔	≥5	✔
Drowsiness	-	<5	✔
Fatigue	-	≥5	✔
Headache	✔	≥5	✔
Insomnia	-	<5	-
Lethargy	-	≥5	-
Lightheadedness	-	<5	✔
Nervousness	-	<5	-
Neuropathy	-	-	✔
Paresthesia	✔	-	✔
Restlessness	✔	-	✔
Syncope	-	-	✔
Tension	-	≥5	-
Vertigo	✔	<5	✔
Weakness	✔	≥5	✔
Xanthopsia	✔	-	-
Dermatological			
Dermatitis	-	-	✔
Hives	-	<5	-
Lyell's syndrome (toxic epidermal necrolysis)	✔	✔	-
Necrotizing angiitis/vasculitis	-	-	✔
Petechiae	-	-	✔
Photosensitivity	✔	-	✔
Pruritus	-	<5	✔
Purpura	✔	-	✔
Rash	✔	<5	✔
Skin necrosis	-	-	✔
Stevens-Johnson syndrome	-	-	✔
Toxic epidermal necrolysis	-	-	✔
Urticaria	✔	-	✔
Vasculitis	✔	<5	-
Endocrine and Metabolic			
Glycosuria	✔	<5	✔
Hepatitis	-	-	✔
Hypercalcemia	✔	✔	✔
Hyperglycemia	✔	<5	✔
Hyperlipidemia	✔	-	-
Hypertonia	-	<5	-
Hyperuricemia	✔	<5	✔
Hypoglycemia	-	-	-
Hypokalemia	✔	3-7	✔
Hypomagnesemia	✔	✔	✔
Hyponatremia	✔	<5	-
Hypophosphatemia	-	-	✔
Peripheral edema	-	<5	-
Gastrointestinal			
Abdominal pain	-	<5	✔
Anorexia	✔	<5	✔
Constipation	✔	<5	✔

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Cramping	✔	-	-
Diarrhea	✔	<5	✔
Dry mouth	-	<5	✔
Dyspepsia	-	<5	-
Epigastric distress	-	-	✔
Gastric irritation	✔	<5	-
Hepatitis	-	-	✔
Jaundice (intrahepatic cholestatic)	✔	-	✔
Nausea	✔	<5	✔
Pancreatitis	✔	-	✔
Vomiting	✔	<5	✔
Genitourinary			
Impotence	✔	<5	✔
Nocturia	-	<5	✔
Polyuria	-	<5	-
Hematologic			
Agranulocytosis	✔	-	✔
Aplastic anemia	✔	-	✔
Leukopenia	✔	-	✔
Thrombocytopenia	✔	-	✔
Laboratory Test Abnormalities			
Elevated blood urea nitrogen	-	<5	✔
Elevated creatinine	-	-	✔
Hypochloremia	-	<5	✔
Musculoskeletal			
Acute gouty attacks	-	-	✔
Back pain	-	≥5	-
Joint pain	-	-	✔
Muscle spasm	✔	≥5	✔
Respiratory			
Cough	-	<5	-
Pharyngitis	-	<5	-
Rhinitis	-	≥5	-
Sinusitis	-	<5	-
Other			
Asthenia	-	<5	-
Chills	-	-	✔
Conjunctivitis	-	<5	-
Infection	-	≥5	-
Tingling of extremities	-	<5	-
Weight loss	-	<5	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the thiazide-like diuretics are summarized in Table 7.

Table 7. Usual Dosing for the Thiazide-like Diurectics[3-9]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chlorthalidone	Edema: Initial, 30 to 60 mg/day or 60 mg on alternate days; maintenance, 90 to 120 mg on alternate days or 120 mg/day	Safety and efficacy in children have not been established.	Tablet: 15 mg 25 mg

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertension: Initial, 15 to 30 mg/day; maintenance, 45 to 50 mg/day		50 mg 100 mg
Indapamide	Edema: Initial, 2.5 mg/day; maintenance, 2.5 to 5 mg/day Hypertension: Initial, 1.25 mg/day; maintenance, 2.5 to 5 mg/day	Safety and efficacy in children have not been established.	Tablet: 1.25 mg 2.5 mg
Metolazone	Edema: 5 to 20 mg/day Hypertension: Initial, 2.5 to 5 mg/day, maintenance, 5 to 20 mg/day	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the thiazide-like diuretics are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Thiazide-like Diuretics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
SHEP Cooperative Research Group[22] and Kostis et al[23] SHEP Chlorthalidone 12.5 mg QD vs placebo Drug dosage was doubled for patients failing to achieve SBP goal at follow-up visits (goal SBP in patients with SBP 180 mm Hg initially was <160 mm Hg; patients with SBP 160 to 179 mm Hg initially, goal was a reduction of at least 20 mm Hg). If SBP goal was not reached with chlorthalidone 25 mg QD, atenolol 25 mg QD or matching placebo was added to the drug regimen. Reserpine 0.05 mg QD or matching	DB, MC, PC, RCT Patients aged ≥60 years with SBP between 160 and 219 mm Hg and DBP <90 mm Hg	N=4,736 Mean 4.5 years	Primary: Total stroke Secondary: Sudden or rapid cardiac death (defined as death within 1 hour or within 1 to 24 hours of the onset of severe cardiac symptoms), nonfatal or fatal myocardial infarction, other cardiovascular death, transient ischemic attack	Primary: With a mean follow-up of 4.5 years, incident of stroke was diagnosed in 103 patients in the active treatment group compared to 159 patients in the placebo group (RR, 0.64; 95% CI, 0.5 to 0.82; *P*=0.0003). Stroke incidence was lower in patients taking active treatment compared to placebo in all baseline age groups: 60 to 69 years, 34 vs 47 events, respectively 70 to 79 years, 48 vs 74 events, respectively 80+ years, 21 vs 38 events, respectively. The results were stratified according to whether patients had had previous antihypertensive therapy or not. In both stratified groups, there was a decrease in the risk of stroke with active treatment compared to placebo. For patients who were not receiving antihypertensive medication at initial contact, the RR, of stroke was 0.69 (95% CI, 0.51 to 0.95; *P*=0.02). For patients who had been receiving antihypertensive medication at initial contact, the RR, of stroke was 0.57 (95% CI, 0.38 to 0.85; *P*=0.01). Secondary: There were 23 sudden and 21 rapid deaths in the active treatment group compared to 23 sudden and 24 rapid deaths in the placebo group (RR, 1.00; 95% CI, 0.56 to 1.78 vs RR, 0.87; 95% CI, 0.48 to 1.56, respectively; *P* values not reported). There were 50 nonfatal and 15 fatal myocardial infarctions in the active treatment group compared to 74 nonfatal and 26 fatal myocardial infarctions in the placebo group (RR, 0.67; 95% CI, 0.47 to 0.96 vs RR, 0.57; 95% CI, 0.30 to 1.08, respectively; *P* values not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo was substituted in patients with contraindications to atenolol.				There were 21 other cardiovascular deaths in the active treatment group compared to 25 in the placebo group (RR, 0.87; 95% CI, 0.49 to 1.55; *P* value not reported). There were 62 transient ischemic attacks in the active treatment group compared to 82 in the placebo group (RR, 0.75; 95% CI, 0.54 to 1.04; *P* value not reported). In the combined endpoints, the RR, of nonfatal myocardial infarction or coronary heart disease death was 0.73 (95% CI, 0.57 to 0.94), coronary heart disease was 0.75 (95% CI, 0.60 to 0.94), cardiovascular disease was 0.68 (95% CI, 0.58 to 0.79). *P* values were not reported. The RR, for atenolol were 0.84 (95% CI, 0.54 to 1.30) for death, 1.34 (95% CI, 0.80 to 2.28) for stroke, and 1.07 (95% CI, 0.71 to 1.61) for cardiovascular disease. *P* values were not reported. The RR, for reserpine were 0.65 (95% CI, 0.26 to 1.59) for death, 0.27 (95% CI, 0.04 to 2.26) for stroke, and 0.55 (95% CI, 0.20 to 1.49) for cardiovascular disease. *P* values were not reported.
Akram et al[24] NATIVE Indapamide SR 1.5 mg QD plus background therapy	Design not specified Patients remaining hypertensive (145-180/95-105 mm Hg) while receiving an angiotensin converting enzyme inhibitor, β-blocker, calcium-channel blocker, angiotensin II receptor blocker, α-blocker, or other therapy	N=1,941 3 months	Primary: Blood pressure Secondary: Glucose and cholesterol levels	Primary: At 3 months, SBP and DBP both decreased significantly compared to baseline. SBP had a change from 166±16 mm Hg at baseline to 132±12 mm Hg at 3 months. DBP had a change from 102±8 mm Hg at baseline to 83±6 mm Hg at 3 months (*P*<0.0001 for both). At study end, 84% of patients achieved target SBP of ≤140 mm Hg and 61% achieved blood pressure normalization (SBP/DBP <140/90 mm Hg; *P* value not reported). Secondary: Glucose and cholesterol levels were unaffected by indapamide SR.
Baguet et al[25] Antihypertensive drugs	MA 80 randomized, double-	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (–19.2 mm Hg;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
considered for inclusion were HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, candesartan cilexetil*, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan, and aliskiren Although the diuretics cicletanine*, furosemide, and spironolactone were considered for inclusion, none of the studies relating to these agents satisfied all inclusion criteria.	blind trials where the drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages including patients aged >18 years with mild or moderate essential hypertension (SBP blood pressure 140–179 mm Hg and/or DBP 90–109 mm Hg)		and DBP Secondary: Not reported	95% CI, –20.3 to –18.0), calcium channel blockers (–16.4 mm Hg; 95% CI, –17.0 to –15.8) and angiotensin converting enzyme inhibitors (–15.6 mm Hg; 95% CI, –17.6 to –13.6) produced the greatest reductions in SBP from baseline (*P* values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (–11.4 mm Hg; 95% CI, –12.0 to –10.9), calcium channel blockers (–11.4 mm Hg; 95% CI, –11.8 to –11.1), and diuretics (–11.1 mm Hg; 95% CI, –11.7 to –10.5). *P* values were not reported. The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: –19.2 mm Hg (95% CI, –20.3 to –18.0) and –11.1 mm Hg (95% CI, –11.7 to –10.5), respectively. β-Blockers: –14.8 mm Hg (95% CI, –15.9 to –13.7) and –11.4 mm Hg (95% CI, –12.0 to –10.9), respectively. Calcium channel blockers: –16.4 mm Hg (95% CI, –17.0 to –15.8) and –11.4 mm Hg (95% CI, –11.8 to –11.1), respectively. Angiotensin converting enzyme inhibitors: –15.6 mm Hg (95% CI, –17.6 to –13.6) and –10.8 mm Hg (95% CI, –11.9 to –9.7), respectively. Angiotensin II receptor antagonists: –13.2 mm Hg (95% CI, –13.6 to –12.9) and –10.3 mm Hg (95% CI, –10.5 to –10.1), respectively. Renin inhibitor: –13.5 mm Hg (95% CI, –14.2 to –12.9) and –11.3 mm Hg (95% CI, –11.7 to –10.9), respectively. *P* values not reported. Secondary: Not reported
Pupita et al[26] Chlorthalidone 50 mg QD vs furosemide 25 mg QD	RCT, SC, XO Men and women with a mean age of 53.9±9.2 years with mild to moderate hypertension	N=36 12 months	Primary: Blood pressure Secondary: Plasma electrolytes, adverse events	Primary: Patients taking chlorthalidone had significantly lower SBP at each monthly measurement compared to baseline ($P<0.01$). However, only DBP values at month 5 were significant compared to baseline ($P<0.05$). Patients taking furosemide had significantly lower SBP at months 3, 4, and 5 compared to baseline ($P<0.05$ for month 3, and $P<0.01$ for months 4 and 5). DBP values were significantly lower at all monthly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				measurements compared to baseline in patients taking furosemide (*P*<0.01). At month 1, SBP decreased by 19.4 mm Hg with chlorthalidone and by 21.2 mm Hg with furosemide (*P*<0.001). DBP decreased by 11 mm Hg with chlorthalidone and by 12.6 mm Hg with furosemide at month 1 (*P*<0.001). Secondary: There were no significant changes in serum sodium levels with either chlorthalidone or furosemide. Patients taking chlorthalidone had significantly lower serum chloride levels compared to baseline at all points (*P*<0.01), whereas patients taking furosemide had significantly lower levels only at month 6 (*P*<0.05). Both chlorthalidone and furosemide significantly reduced serum potassium levels at all points compared to baseline (*P*<0.01). Patient taking chlorthalidone reported adverse effects including dizziness, transient abdominal disorder, and slight weakness. Patients taking furosemide reported transient early weakness and irritability. The rate of adverse events was not statistically significant in either treatment group (*P* value not reported).
Ernst et al[27] HCTZ 25 mg QAM vs chlorthalidone 12.5 mg QAM At week 4, both HCTZ and chlorthalidone were titrated to 50 mg QAM and 25 mg QAM, respectively for the remainder of the study.	Active-treatment, RCT, SB, XO Men and women aged 18 to 79 years with prehypertension or a new or established diagnosis of hypertension (stage 1 or 2), not receiving antihypertensive medications, and had an average office blood pressure value in the last 6 months between 140	N=30 8 weeks plus 4 week washout period	Primary: Comparison of the change in 24-hour mean SBP and DBP from baseline to week 8 Secondary: Comparison of changes in mean SBP and mean DBP for office blood pressure at each visit, change in ambulatory	Primary: At week 8, there was a greater reduction in 24-hour mean SBP with chlorthalidone 25 mg/day compared to HCTZ 50 mg/day compared to baseline (−12.4±1.8 vs −7.4±1.7 mm Hg, respectively; *P*=0.054). Secondary: There was a trend in favor of greater reduction in SBP with chlorthalidone than with HCTZ at each office visit. However, the difference was only statistically significant at week 2 (−15.7±2.2 vs −4.5±2.1 mm Hg, respectively; *P*=0.001). Although mean reductions in DBP was also greater with chlorthalidone compared to HCTZ at each study visit, the differences were not statistically significant at any visit (*P*>0.89 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and 179 mm Hg systolic or 90 and 109 mm Hg diastolic		daytime and nighttime mean SBP and DBP from baseline to week 8, development of hypokalemia (defined as serum potassium <3.5 mEq/L	The reduction in SBP during nighttime hours was −13.5±1.9 mm Hg for chlorthalidone and −6.4±1.7 mm Hg for HCTZ (*P*=0.009). The reduction in daytime mean SBP between both groups was not significantly different (−11.4±2.0 vs −8.1±1.9 mm Hg, respectively; *P*=0.230). Changes in serum potassium were similar between treatment groups (*P*=0.76). The incidence of hypokalemia was 50% in patients taking HCTZ and 46% in patients taking chlorthalidone (*P*=0.682).
Carter et al[28] Chlorthalidone 12.5 to 600 mg/day vs HCTZ 12.5 to 450 mg/day	MA Included studies which evaluate the pharmacokinetic and blood pressure lowering effects of chlorthalidone and HCTZ	N=200 Duration varied per study	Primary: Blood pressure Secondary: Serum potassium	Primary: In a dose equivalence study comparing HCTZ 100 mg QD to chlorthalidone 50 mg QD, blood pressure (SBP/DBP) reduced by 18/8 and 25/10 mm Hg compared to baseline, respectively (*P* value not reported). In another study comparing HCTZ 25 mg and triamterene 50 mg QD, HCTZ 50 mg and triamterene 100 mg QD, and chlorthalidone 50 mg QD, the blood pressure reduction was 15/8, 18/12, and 25/16 mm Hg, respectively (*P* value not reported). One other dose equivalence study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, blood pressure reduction was 22/16 and 18/15 mm Hg, respectively (*P* values not reported). All available studies were inspected and it was concluded that HCTZ 50 mg is approximately equivalent to chlorthalidone 25 to 37 mg. Furthermore, it was suggested that chlorthalidone doses should generally be approximately 50% to 75% of the typical HCTZ dose. Secondary: In a study comparing HCTZ 100 mg QD and chlorthalidone 50 mg QD, potassium increased slightly with chlorthalidone (0.02 mEq/L) and decreased significantly with HCTZ (0.22 mEq/L; *P*=0.009). However, in another study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, serum potassium decreased by 0.38 mEq/L

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				with HCTZ and by 0.03 mEq/L with chlorthalidone. The difference was not statistically significant (*P*<0.07).
Milia et al[29] Indapamide 2.5 mg QD vs bendroflumethiazide* 2.5 mg QD	DB, PG, PRO, RCT Ambulant patients with a first-ever minor hemispheric ischemic stroke or transient ischemic attack	N=26 28 days	Primary: Blood pressure, cerebral blood flow Secondary: Not reported	Primary: Both indapamide and bendroflumethiazide significantly reduced blood pressure from baseline (−14.7±12.5 mm Hg and −7.7±9.16 mm Hg, respectively; *P*<0.001 and *P*=0.02, respectively). A nonsignificant trend toward greater blood pressure reduction was seen in patients taking indapamide. There were no statistically significant differences in blood pressure reduction between both treatment groups (*P* value not reported). There was a nonsignificant trend toward increases in blood flow in both treatment groups. However, there was no statistically significant differences in carotid blood flow between both treatment groups (*P*=0.04 for between-group comparison). Secondary: Not reported
Madkour et al[30] HCTZ 50 mg QD vs indapamide 2.5 mg QD	RCT Patients aged 32 to 70 years with impaired renal function for 1 to 15 years and moderate hypertension for 2 to 27 years, initial creatinine clearance between 32 and 80 mL/min/1.73 m^2 body surface area	N=28 24 months	Primary: Blood pressure, changes in creatinine clearance Secondary: Not reported	Primary: Blood pressure normalized in all patients taking either indapamide or HCTZ. There were no significant differences in SBP or DBP between groups (*P* value not reported). At 24 months, creatinine clearance progressively increased from 58±4.4 to 72±4.4 mL/min/1.73 m^2 body surface area in patients treated with indapamide (*P*<0.01). However, creatinine clearance progressively decreased from 65±3.0 to 53±3.0 mL/min/1.73 m^2 body surface area in patients treated with HCTZ (*P*<0.01). Therefore, creatinine clearance significantly increased by 28.5±4.4% with indapamide and decreased by 17.4±3.0% with thiazide therapy (*P*<0.01). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Ames[31] ≤25 mg of HCTZ or its equivalent in other thiazides, up to 112.5 mg QD vs indapamide 2.5 mg QD HCTZ was the most commonly studied thiazide; therefore, all other thiazides were expressed as approximate mg equivalents of HCTZ.	MA 13 clinical trials evaluating the effects of thiazides and indapamide on blood lipids and blood pressure as monotherapy for hypertension	N=1,547 1 to 25 months	Primary: Comparison of the effects of thiazides and indapamide on blood lipids and blood pressure Secondary: Not reported	Primary: The mean change from baseline was 1.4% for total cholesterol, 5.5% for high density lipoprotein cholesterol, and ─0.5% for triglycerides with indapamide. None of the differences were statistically significant (*P* value not reported). Low-dose thiazide therapy did not decrease total cholesterol at any data point. The mean percent increase in total cholesterol was 3.8%, in high density lipoprotein cholesterol was 3.1%, and in triglycerides was 10.8% with low-dose HCTZ. The increases in total cholesterol and triglycerides from baseline was statistically significant ($P<0.01$). The mean change in total cholesterol was 6.3%, in high density lipoprotein cholesterol was ─0.5%, and in triglycerides was 19.5% for higher doses of HCTZ. Increases from baseline in total cholesterol and triglycerides were statistically significant (*P* value not reported). SBP decreased more with higher doses of HCTZ than with low-dose thiazide therapy ($P<0.05$). The effects of indapamide on systolic arterial pressure were intermediate between, and not statistically different from, either thiazide dose. Decreases in DBP did not differ among groups (*P* value not reported). Secondary: Not reported
Hua et al[32] Chlorothiazide 0 to 5 g BID vs metolazone 5 mg QD	XO Patients with hypertension	N=20 Duration not specified	Primary: Blood pressure, serum potassium Secondary: Not reported	Primary: Blood pressures on metolazone tended to be lower than on chlorothiazide, but the difference was not statistically significant (*P* values not reported). Both agents significantly lowered serum potassium concentrations and total body potassium to a similar degree. However, the serum potassium did not fall below the normal range in any patient and no potassium supplements were required (*P* values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
ALLHAT Collaborative Research Group[33] ALLHAT Chlorthalidone 12.5 to 25 mg/day vs amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day	AC, DB, MC, RCT Patients aged 55 years or older who had stage 1 or stage 2 hypertension with ≥1 additional risk factor for coronary heart disease events (including previous myocardial infarction or stroke >6 months ago, left ventricular hypertrophy or echocardiography, history of type 2 diabetes, current cigarette smoking, high density lipoprotein cholesterol <35 mg/dL, or documentation of other atherosclerotic cardiovascular disease)	N=33,357 4 to 8 years (mean 4.9 years)	Primary: Fatal coronary heart disease or nonfatal myocardial infarction combined Secondary: All cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease, cancer, end-stage renal disease	Primary: There was no significant difference in the primary outcome between amlodipine and chlorthalidone treatments, or between lisinopril and chlorthalidone (risk ratio 0.98; 95% CI, 0.90 to 1.07; *P*=0.65 and risk ratio 0.99; 95% CI, 0.91 to 1.08; *P*=0.81). Secondary: The secondary endpoints did not differ between amlodipine and chlorthalidone for all-cause mortality, combined coronary heart disease, stroke, combined cardiovascular disease, angina, coronary revascularization, peripheral arterial disease, cancer, or end-stage renal disease. However, heart failure and hospitalized/fatal heart failure, components of combined cardiovascular disease, occurred at higher rates with amlodipine than with chlorthalidone (risk ratio 1.38; 95% CI, 1.25 to 1.52; *P*<0.001 and risk ratio 1.35; 95% CI, 1.21 to 1.50; *P*<0.001, respectively). In a comparison of lisinopril to chlorthalidone, the secondary endpoints of all-cause mortality, combined coronary heart disease, peripheral arterial disease, cancer, or end-stage renal disease did not significantly differ between treatment groups. However, there were higher rates of stroke (risk ratio 1.15; 95% CI, 1.02 to 1.30; *P*=0.02), combined cardiovascular disease (risk ratio 1.10; 95% CI, 1.05 to 1.16; *P*<0.001), heart failure (risk ratio 1.19; 95% CI, 1.07 to 1.31; *P*<0.001), angina (hospitalized or treated [risk ratio 1.11; 95% CI, 1.03 to 1.20; *P*=0.01]), and coronary revascularizations (risk ratio 1.10; 95% CI, 1.00 to 1.21; *P*=0.05) observed in the lisinopril group compared to the chlorthalidone group.
Karotsis et al[34] Chlorthalidone 12.5 mg QD plus diltiazem 240 mg QD vs	RCT Patients aged 25 to 79 years with uncontrolled hypertension (defined as average office blood pressure greater than	N=211 8 weeks	Primary: Blood pressure Secondary: Not reported	Primary: There was a significant decline in both office and home SBP and DBP during the study period for all treatment groups. The antihypertensive effect was more pronounced and reached statistical significance when home blood pressure monitoring was used in comparison to office blood pressure without the white-coat effect

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
felodipine 5 mg QD plus diltiazem 240 mg QD vs lisinopril 10 mg QD plus diltiazem 240 mg QD vs valsartan 80 mg QD plus diltiazem 240 mg QD	140/90 mm Hg for all or 153/85 mm Hg for diabetics or subjects under the age of 65, confirmed on 2 office visits at least 1 week apart) after at least 4 weeks of open monotherapy with diltiazem at 240 mg QD			(*P*<0.001 for all blood pressure changes). With or without the white-coat effect, blood pressure still declined and the differences were statistically significant (*P*<0.0001 for all blood pressure changes). Secondary: Not reported

*Agent not available in the United States (US)
Drug regimen abbreviations: QAM=every morning, QD=once daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single blinded, SC=single centre, SR=sustained release, XO=crossover
Other abbreviations: β-blockers=β-adrenergic blocking agents, CCBs=calcium channel blocking agents, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Thiazide-like Diuretics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
chlorthalidone	tablet	Hygroton*†, Thalitone	$$	$
indapamide	tablet	Lozol®*†	N/A	$
metolazone	tablet	Zaroxolyn®*	$$$	$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

All thiazide-like diuretics within this review are Food and Drug Administration (FDA)-approved for the management of edema associated with congestive heart failure or various other conditions. They are also FDA-approved for the treatment of hypertension either as monotherapy or in combination with other antihypertensive agents.[3-8] No head-to-head clinical trials comparing the efficacy of the thiazide-like diuretic agents to each other for their FDA approved indications were identified. However, clinical trials comparing thiazide-like diuretics to thiazide diuretics have demonstrated comparable efficacy.[27-32] Chlorthalidone, indapamide, and metolazone have all exhibited reductions in blood pressure from baseline similar to those seen with the comparator drugs, hydrochlorothiazide or chlorothiazide.[27-28,30-31]

For the treatment of edema related to congestive heart failure, the American College of Cardiology/American Heart Association (ACC/AHA) recommends diuretics. Diuretics and salt restriction are indicated in patients with current or previous symptoms of heart failure and evidence of fluid retention due to reduced left ventricular ejection fraction. A thiazide-type diuretic, including thiazide and thiazide-like diuretics, may be preferred in hypertensive heart failure patients with mild fluid retention as a result of more persistent antihypertensive effects.[1] Diuretics are also recommended by the ACC/AHA in patients with heart failure and normal left ventricular ejection fraction to control pulmonary congestion and peripheral edema. Similar recommendations have been made by the Heart Failure Society of America (HFSA).[12] In addition, the HFSA indicates that metolazone or chlorothiazide may be given to patients with persistent fluid retention despite high dose therapy with loop diuretics.[12] In addition, metolazone may also be beneficial in patients with glomerular filtration rates <20 mL/min.[11]

In regards to the treatment of hypertension, the major national guidelines including the Seventh Report of the Joint National Committee (JNC 7), all recommend that a diuretic agent should be considered as initial therapy.[2,14,16-17] More specifically, the JNC 7 guidelines and the Medical Letter recommend a thiazide-type diuretic, including thiazide and thiazide-like diuretics, as initial therapy in many patients with uncomplicated hypertension as monotherapy or in combination with other antihypertensive agents.[2,16] The National Institute for Health and Clinical Excellence (NICE) guidelines also recommend thiazide-type diuretics as first-line, but only in those aged 55 years or older.[17]

In patients with hypertensive chronic kidney disease, diuretics should be a component of the antihypertensive regimen in most patients. Thiazide-type diuretics, including thiazide and thiazide-like diuretics, are recommended when glomerular filtration rates are ≥30 mL/min/1.73 m^2.[21] In patients with glomerular filtration rates <30 mL/min/1.73 m^2, loop diuretics would be preferred due to the minimal effectiveness of thiazide-type diuretics on extracellular fluid volumes reductions at lower glomerular filtration rates.[21] However, because metolazone does not significantly decrease renal plasma flow and exerts its effects at different sites other than the distal tubule, patients with resistance to loop diuretics or have glomerular filtration rates <20 mL/min may benefit from a combination of metolazone and a loop diuretic.[11,21]

In general, the thiazide-like diuretics share similar drug interactions and adverse events. Currently all agents in this class are available in a generic tablet dosage form. Based on the current literature and clinical guidelines on the use of thiazide-like diuretics, one particular single entity agent is not preferred over another.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand thiazide-like diuretics is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Acute Myocardial Infarction
September 10, 2008

I. Overview

Acute myocardial infarction (MI) is a clinical acute coronary syndrome resulting from obstruction of a coronary artery. Different degrees of obstruction result in different outcomes, which can include unstable angina, non–ST-segment-elevation MI (NSTEMI), and ST-segment elevation MI (STEMI). ST-segment elevation refers to elevations of the ST-segment on echocardiogram (ECG); Q waves may or may not be present.[1] ST-segment elevations and Q waves are absent in an NSTEMI.[1] Myocardial necrosis results from the reduction in oxygen supply to the infarcted tissue. Atherosclerosis of the coronary arteries is an essential part of this process in most cases. Infarction may occur when an atherosclerotic plaque erodes or ruptures, causing thrombosis formation, or when cardiac work exceeds the ability of the coronary artery to meet the metabolic needs of the myocardium. According to the American Heart Association, each year 1.2 million people experience an MI in the United States. In 2004, approximately 451,000 people succumbed to coronary heart disease (CHD)-related deaths, with approximately 157,000 resulting from an MI.[2] Treatment guidelines for acute MI can be found in Table 1.

II. Evidence-Based Medicine and Current Treatment Guidelines

Table 1. Current Treatment Guidelines for Acute Myocardial Infarction

American College of Cardiology (ACC)/American Heart Association (AHA): 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)[3]
Initial and Hospital Management • Oxygen, morphine, nitroglycerin (NTG), angiotensin-converting enzyme inhibitors (ACE inhibitors), β-adrenergic blocking agents (β-blockers), and aspirin may be used in patients presenting with an MI. Patients should be considered for reperfusion therapy. • All patients should continue receiving β-blockers unless contraindicated. • Patients that did not receive β-blockers within 24 hours of ST-Elevation Myocardial Infarction (STEMI) should be started on these agents unless contraindicated. • Patients with early contraindications to β-blockers should be reevaluated for candidacy for β-blocker therapy. • Patients with moderate or severe left ventricular failure should receive β-blockers as secondary prevention and the dose should be titrated slowly. • Patients undergoing facilitated percutaneous intervention (PCI), may be treated with high dose aspirin, GP (glycoprotein) IIb/IIIa receptor inhibitors, and/or fibrinolytic therapy. • Clopidogrel should be initiated with aspirin and continued for 14 days regardless of whether reperfusion with fibrinolytic therapy is performed. • Long-term maintenance therapy with clopidogrel for up to 12 months may be reasonable. Secondary Prevention • Smoking cessation is advised, in addition to avoidance of secondhand smoke. • Patients with co morbid hypertension should be treated initially with β-blockers and/or ACE inhibitors with the addition of other medication as needed to achieve a blood pressure goal of <140/90 mm Hg (or <130/80 mm Hg in patients with diabetes or chronic kidney disease). • It may be reasonable to encourage the consumption of omega-3 fatty acids in the form of food or capsules. • Low-density lipoprotein cholesterol (LDL-C) levels should be maintained at <100 mg/dL; <70 mg/dL is also

reasonable. If LDL-C levels are ≥100 mg/dL, LDL-C lowering therapy should be initiated.

- Niacin, fibric acid derivatives (fibrates), or more intensive LDL-C lowering therapy may be beneficial in lowering non–high-density lipoprotein cholesterol (non–HDL-C) levels.
- Physical activity and weight management should be encouraged.
- Aspirin therapy is recommended (unless contraindicated) at a dose of 162-325 mg for all patients post-PCI for at least 1 month after bare metal stent implantation, 3 months for sirolimus-eluting stent placement, and 6 months after paclitaxel-eluting stent placement. Thereafter, aspirin should be continued indefinitely at 75-362 mg.
- Clopidogrel should be given for at least 12 months to patients who have had a drug-eluting stent placed, and for a minimum of 1 month and ideally up to 12 months after placement of a bare-metal stent. If the patient is at a high risk of bleeding, it should be given for at least 2 weeks.
- Clopidogrel should be given for at least 14 days to patients not undergoing stent placement.
- Long-term therapy with clopidogrel up to 12 months is reasonable in patients regardless of whether or not they receive reperfusion therapy.
- Initiating and managing warfarin to an international normalized ratio (INR) of 2.0-3.0 is recommended in post-MI patients with atrial fibrillation or flutter when clinically indicated. When therapy with aspirin, clopidogrel, and warfarin is indicated, an INR of 2.0-2.5 is recommended.
- ACE inhibitors are recommended in all patients with a left ventricular ejection fraction ≤ 40%, and those with hypertension, diabetes, or chronic kidney disease unless contraindicated.
- ACE inhibitors are reasonable in patients with normal left ventricular function and well-controlled cardiovascular risk factors.
- ARBs are recommended in patients who are intolerant to ACE inhibitors and have heart failure or who have a left ventricular ejection fraction of ≤ 40%.
- ARBs should be considered in all patients intolerant to ACE inhibitor therapy.
- Combination therapy with ARBs and ACE inhibitors may be considered in patients with systolic dysfunction heart failure.
- β-Blockers should be initiated and continued in all patients who have had an MI, acute coronary syndrome (ACS), or left ventricular dysfunction with or without heart failure symptoms (unless contraindicated).
- Annual influenza vaccination is recommended for all patients with cardiovascular disease (CVD).

National Institute for Health and Clinical Excellence (NICE): Post-Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007) [4]

- The following medications are recommended for all patients who have had an MI: an ACE inhibitor, aspirin, β-blockers, and a hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin).
- ACE inhibitors are recommended early after presentation with an acute MI.
- ARBs are recommended in patients who are intolerant to ACE inhibitor therapy.
- Combination therapy with an ACE inhibitor and an ARB is not routinely recommended.
- Patients with a proven MI in the past and with heart failure and left ventricular systolic failure, treatment should be in line with recommendations for chronic heart failure.
- In patients with a proven MI in the past and with asymptomatic left ventricular systolic dysfunction and in those without heart failure and preserved left ventricular function, ACE inhibitors are recommended (ARBs may be given to patients who are intolerant of ACE inhibitors).
- Aspirin is recommended in all patients after an MI and should be continued indefinitely.
- Clopidogrel combined with low-dose aspirin for 12 months is recommended in patients who have had a non–ST-segment-elevation ACS and who are at moderate-to-high risk of MI or death. Thereafter, patients may be treated with aspirin without clopidogrel in the absence of indication for dual antiplatelet therapy.
- Patients who have been treated with aspirin and clopidogrel within the first 24 hours of an STEMI should continue on dual antiplatelet therapy for at least 4 weeks. Thereafter, clopidogrel may be discontinued in the absence of indication for dual antiplatelet therapy.
- Patients not treated with both clopidogrel and aspirin within 24 hours of an MI should not be routinely treated with dual antiplatelet therapy.
- Dual antiplatelet therapy with aspirin and clopidogrel should not be used for longer than 12 months unless another indication for dual antiplatelet therapy exists. After an STEMI, the combination of aspirin and clopidogrel is usually

shorter than 12 months.

- Clopidogrel monotherapy may be used in patients intolerant to aspirin.
- Low-dose aspirin and a proton-pump inhibitor are recommended in patients with co morbid dyspepsia.
- All patients should be offered treatment with a β-blocker after an MI. Patients with left ventricular systolic dysfunction and/or heart failure should be managed according to recommendations for chronic heart failure. Clinicians may want to consider use of a β-blocker which is licensed for use in heart failure.
- After a proven MI in the past, asymptomatic patients with preserved left ventricular function should not routinely be offered a β-blocker unless they are at risk for further cardiovascular events or other compelling indications exist.
- Patients being treated with warfarin for another indication should continue on warfarin. Those being treated with moderate intensity warfarin (INR 2.0-3.0), at a low risk of bleeding, may be treated with aspirin.
- Calcium-channel blocking agents (CCBs) should not routinely be used to reduce cardiovascular risk after an MI.
- Verapamil or diltiazem may be considered for secondary prevention in patients without pulmonary congestion or left ventricular systolic dysfunction in whom β-blockers must be discontinued or in whom β-blockers are contraindicated.
- Aldosterone antagonists licensed for use after an MI should be initiated within 14 days of an MI in patients with heart failure and left ventricular systolic dysfunction, preferably after ACE inhibitor initiation.
- Patients who have had a proven MI in the past and have heart failure due to left ventricular systolic dysfunction, treatment should be in line with recommendations for chronic heart failure.
- Statins are recommended in patients who have had an MI and should be offered to patients as soon as possible.
- If statin therapy is contraindicated, other lipid-lowering drugs should be considered.

European Society of Cardiology (ESC): Management of Acute Myocardial Infarction in Patients Presenting With ST-segment Elevation (2003)[5]

Prophylactic Therapies in the Acute Phase

- Administer aspirin 150-325 mg.
- Oral β-blockers should suffice in most cases. An intravenous (IV) β-blocker may be used especially in tachycardia (in absence of heart failure), relative hypertension and pain unresponsive to opiates unless contraindicated.
- ACE inhibitor should be initiated within 24 hours.
- Routine use of lidocaine is not justified due to an increased risk of asystole.
- Routine use of nitrates in the initial phase of MI has not shown to be of convincing value and is not recommended.
- There is no case for using CCBs for prophylactic purposes in the acute phase of an MI.
- Recent trials have failed to demonstrate that the use of magnesium provides a benefit, and it is not recommended for routine use.

Secondary Prevention

- Smoking cessation is advised.
- Aspirin 75-160 mg day is recommended. Clopidogrel 75 mg daily may be used if aspirin is not tolerated.
- β-blockers are recommended for all patients unless contraindicated.
- Diltiazem or verapamil may be appropriate if β-blockers are contraindicated in the absence of heart failure.
- Dihydropyridines have not been shown to improve prognosis and should only be used for clear clinical indications.
- ACE inhibitors should be continued unless contraindicated.
- Statins are recommended if total cholesterol is >190 mg/dL and/or LDL-C >115 mg/dL despite therapeutic lifestyle changes.
- Fibrates may be used if HDL-C ≤ 45 mg/dL and triglycerides ≥ 200 mg/dL.
- Nitrates should be used only in the presence of angina pectoris.

Blood pressure is reported as mm Hg with the first number being systolic pressure and second number being diastolic pressure.

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Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Angina Pectoris
September 10, 2008

I. Overview

Angina pectoris is a symptom of myocardial ischemia, and as a clinical syndrome is characterized by chest pain, discomfort, or heaviness which may radiate to the neck, jaw, arm, or back. While chest pain is the classic symptom of angina pectoris, it may present as shortness of breath, fatigue, or other symptom complexes. Myocardial ischemia develops when there is an imbalance between myocardial oxygen supply and demand. Myocardial ischemia may have various causes. Often it is due to coronary artery disease, which may obstruct the coronary arteries and restrict the flow of oxygenated blood to the myocardium. It may also stem from other conditions which cause abnormal constriction of coronary arteries, or it may occur in situations in which the oxygen-carrying capacity of the blood is reduced. The American Heart Association estimates that 9,100,000 Americans, or 4.1% of all Americans, suffer from angina, with 500,000 new cases of stable angina per year.[1,2]

Angina can be classified as stable, unstable or variant angina. Stable angina, also known as chronic stable angina, is usually precipitated by an increase in myocardial oxygen demand, typically as the result of physical exertion or stress, and the onset of the episodes are usually predictable. Such an episode will typically subside with rest or removal of the stressor, or with minimal use of sublingual nitroglycerin. In unstable angina, ischemia may occur at rest and is primarily caused by reductions in coronary blood flow, in contrast to stable angina, where episodes are precipitated by increases in myocardial oxygen demand. Unstable angina is considered an acute coronary syndrome (ACS) and should be treated as a medical emergency. Other ACS includes non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). The primary causes of reduction in blood flow include the rupture of an atherosclerotic plaque in the coronary artery, thrombus formation, and vasoconstriction at the site of the rupture. Variant angina, also known as Prinzmetal's angina, is a form of unstable angina and is caused by a focal vasospasm in a coronary artery.[3,4]

A grading system established by the Canadian Cardiovascular Society (CCS) is widely used to classify the severity of angina. The grading system is summarized below in Table 1.[5]

Table 1. Canadian Cardiovascular Society Grading of Angina Pectoris[5]

Class	Description	Symptoms
Class I	Ordinary physical activity, such as walking and climbing stairs does not cause angina.	Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity.	Angina with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina with walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity.	Angina with walking 1-2 blocks on the level and climbing 1 flight of stairs in normal conditions and at normal pace.
Class IV	Inability to carry on any physical activity without discomfort.	Anginal syndrome may be present at rest.

II. Evidence-Based Medicine and Current Treatment Guidelines

Table 2. Current Treatment Guidelines for Angina Pectoris

American College of Cardiology (ACC)/American Heart Association (AHA): 2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)[6]
• Lifestyle modifications including smoking cessation, limiting secondhand smoke, weight management, increased physical activity, and dietary changes are recommended in all patients with chronic stable angina. • Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin-converting enzyme (ACE) inhibitors and/or β-adrenergic blocking agents (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 mm Hg or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Dietary therapy, physical activity, adding plant sterols/stanols, and consuming omega-3 fatty acids are recommended for all patients to control lipid levels. Low-density lipoprotein cholesterol (LDL-C) levels should be <100 mg/dL, with possible reductions to <70 mg/dL in certain patients. LDL-C lowering medication should be initiated when LDL-C levels are ≥ 100 mg/dL. • Physical activity of 30-60 minutes 7 days per week is recommended. A medically supervised program such as cardiac rehabilitation is recommended in at-risk patients. • Body mass index should be assessed and maintained between 18.5 kg/m^2 and 24.9 kg/m^2. When waist circumference is ≥ 35 inches in women and ≥ 40 inches in men, lifestyle modifications should be initiated and treatment for metabolic syndrome should be considered. • Lifestyle modification and pharmacotherapy are recommended to achieve near-normal hemoglobin A_{1c} (HbA_{1c}) levels in patients with diabetes. • Aspirin 75-162 mg is recommended in all patients unless contraindicated. Clopidogrel may be used when aspirin is contraindicated. Close monitoring is recommended if warfarin is to be used with aspirin and/or clopidogrel. • ACE inhibitors should be used indefinitely in patients with left ventricular ejection fraction of ≤ 40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal left ventricular ejection fraction in whom cardiovascular risk factors remain well controlled and revascularization has been performed) unless contraindicated. • Angiotensin receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a left ventricular ejection fraction of ≤ 40%. • ARBs may be considered in combination with an ACE inhibitor due to left ventricular systolic dysfunction. • Aldosterone blockers are recommended in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a left ventricular ejection fraction ≤ 40% and have either diabetes or heart failure. • β-Blocker therapy is recommended indefinitely in all patients who have had an MI, acute coronary syndrome (ACS), or left ventricular dysfunction with or without heart failure symptoms unless contraindicated. • All patients with cardiovascular disease should receive an annual influenza vaccine unless contraindicated. • Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) should be recommended even in mild-to-moderate elevations of LDL-C. • Use sublingual nitroglycerin (NTG) or NTG spray for immediate relief of angina. • Long-acting calcium-channel blocking agents (CCBs) or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine CCBs can increase adverse cardiac events and should not be used. • Long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful.

American College of Cardiology (ACC)/American Heart Association (AHA): ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)[7]
• Nitrates, morphine, β-blockers, CCBs, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet agents, and GP IIb/IIIa receptor antagonists can be used in the acute setting during early hospitalization. • All patients with unstable angina should be given sublingual or spray NTG with instructions for proper use. If patients have anginal discomfort and do not get relief within 5 minutes after the first dose of NTG, emergency treatment should be sought by dialing 911 and the patient can take up to 2 additional doses 5 minutes apart. • Patients treated medically without stenting should be treated indefinitely with aspirin 75-162 mg daily and clopidogrel 75 mg daily for at least one month and ideally for up to 1 year. Clopidogrel can be given instead of aspirin in aspirin-allergic patients or aspirin desensitization may be attempted. • Patients treated with bare metal stents should be treated with aspirin 162-325 mg daily for at least 1 month followed by 75-162 mg daily indefinitely. Clopidogrel 75 mg daily should be prescribed for at least 1 month and ideally up to 1 year. If the patient is at high risk of bleeding, the clopidogrel should be given for a minimum of 2 weeks. Clopidogrel can be given instead of aspirin in aspirin-allergic patients or aspirin desensitization may be attempted. • Patients treated with a sirolimus drug eluting stent should be treated with, aspirin 162-325 mg for at least 3 months, and for at least 6 months after a paclitaxel drug-eluting stent. In both cases, the aspirin should be continued indefinitely at 75-162 mg daily. Clopidogrel 75 mg daily should be prescribed for at least 12 months in all patients treated with a drug-eluting stent. Clopidogrel can be given instead of aspirin in aspirin-allergic patients, or aspirin desensitization may be attempted. • Aspirin may be given at a lower dose of 75-162 mg immediately after stenting in patients who are at a high risk of bleeding or when the prescriber is concerned about the risk of bleeding. • Patients who have an additional indication for anticoagulation may be treated with warfarin, monitored and adjusted to achieve an international normalized ratio (INR) of 2.0-3.0. • Warfarin with low-dose aspirin (75-81 mg per day, INR 2.0 to 2.5) or without (INR 2.5 to 3.5) may be reasonable for patients at high coronary artery risk and low bleeding risk who are intolerant of clopidogrel. • Dipyridamole is not recommended as it has not been shown to be effective. • β-Blockers are recommended in all patients unless otherwise contraindicated. Treatment should be initiated acutely or within a few days of the event and continued indefinitely. In patients with moderate-to-severe left ventricular failure, β-blockers should be titrated gradually. • ACE inhibitors should be initiated and continued indefinitely in patients with heart failure, left ventricular dysfunction, diabetes, or hypertension unless contraindicated. ARBs should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and signs of heart failure and left ventricular ejection fraction <40%. • Aldosterone blockers should be initiated in patients without significant renal dysfunction or hyperkalemia who are receiving therapeutic doses of an ACE inhibitor, have a left ventricular ejection fraction <40%, and either symptomatic heart failure or diabetes. • ACE inhibitors are reasonable for all patients, even without left ventricular dysfunction, hypertension, or diabetes unless contraindicated. • ACE inhibitors are reasonable for patients with heart failure and left ventricular ejection fraction <40%. • Patients who cannot tolerate ACE inhibitors may be treated with an ARB if they have signs of heart failure and left ventricular ejection fraction <40%. • Combination ACE inhibitor and ARB therapy may be considered in patients with persistent symptomatic heart failure and left ventricular ejection fraction <40% despite conventional therapy including an ACE inhibitor or ARB alone, unless the patient is already on an aldosterone antagonist. • CCBs are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. • Statins are recommended for all patients, including post-revascularization patients, regardless of baseline LDL-C and diet modification. • LDL-C goals should be <100 mg/dL, with further reductions of <70 mg/dL if desired. • If triglycerides are ≥ 500 mg/dL, therapeutic options to prevent pancreatitis consist of a fibric acid derivative (fibrate) or niacin before LDL-lowering therapy is recommended. LDL-C should be treated to goal after triglycerides lowering therapy. If possible, it is recommended to achieve a non-high density lipoprotein cholesterol (HDL-C) of <130 mg/dL.

- Plant stanols/sterols and/or viscous fiber are reasonable to further lower LDL-C.
- Omega-3 fatty acids in the form of fish in capsule form (1 g per day) for risk reduction may be reasonable. For the treatment of elevated triglycerides, higher doses (2-4 g per day) may be used for risk reduction.
- Blood pressure control is recommended according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).
- For patients with blood pressure ≥ 140/90 mm Hg (or ≥ 130/80 mm Hg for patients with chronic kidney disease or diabetes), it is useful to add blood pressure medication(s) as tolerated, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs such as thiazide diuretics as needed to achieve target blood pressure.
- In patients with diabetes, lifestyle and pharmacological interventions should be initiated to achieve HbA_{1c} levels of <7%.
- Smoking cessation and reduction of exposure to second-hand smoke are recommended.
- Appropriate weight management and physical activity are recommended.
- Annual influenza vaccination is recommended unless otherwise contraindicated.
- Musculoskeletal pain should be treated with acetaminophen, small doses of narcotics, or non-acetylated salicylates. Therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) may be reasonable if the aforementioned medications do not provide adequate relief.
- NSAIDs with increasing degrees of cyclooxygenase-2 (COX-2) selectivity may be considered only when intolerable discomfort persists despite attempts at therapy with acetaminophen, small doses of narcotics, non-acetylated salicylates, or nonselective NSAIDs.
- Treatment with nitrates and CCBs is recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions.
- Nitrates, β-blockers, and CCBs (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.

European Society of Cardiology (ESC): Management of Stable Angina Pectoris (2006)[8]

Therapy to Improve Prognosis

- Angina is graded according to the Canadian Cardiovascular Society described above.
- Patients should seek medical attention if angina persists for more than 10-20 minutes after resting and/or is not relieved by NTG.
- Patients with angina should be counseled on lifestyle modifications including cigarette smoking, diet, and physical activity.
- Low-dose aspirin (75-150 mg daily) is the antithrombotic of choice for most patients. Clopidogrel may be considered in some patients.
- The use of unopposed COX-2 inhibition is not recommended in patients with angina.
- Clopidogrel may be used in patients who are intolerant to aspirin therapy and in combination with aspirin for a finite period of time in patients who have undergone coronary stenting.
- Dipyridamole is not recommended for antithrombotic therapy in patients with stable angina.
- Statin therapy should be considered in patients with stable CAD and stable angina based on their risk level and the benefit of lowering cholesterol to the normal range. Statin doses shown to reduce morbidity/mortality include simvastatin 40 mg, pravastatin 40 mg, and atorvastatin 10 mg. Dosages should be adjusted as needed to achieve lipid goals. High-dose atorvastatin therapy should be reserved for high-risk patients.
- Other lipid-lowering medications like fibrates, nicotinic acid, and combination products may be added to control lipid levels in patients with severe dyslipidemia.
- ACE inhibitors should be considered in patients with stable angina and co morbid hypertension, diabetes, heart failure, asymptomatic left ventricular dysfunction, and patients who have had an MI. Patients with stable angina who do not have an indication for an ACE inhibitor may be treated with one if the benefits of the agent (possible absolute risk reduction) outweigh the possible side effects.
- β-blockers are recommended as first-line therapy in patients with angina in the absence of contraindications.
- CCBs may be recommended in patients with angina who cannot tolerate β-blockers and who have had an MI and who do not have heart failure.

Symptomatic Treatment and Treatment of Ischemia

- NTG should be prescribed for patients for symptom relief and situational prophylaxis. Instructions for proper use should also be provided.
- β-blockers should be titrated to full dose. Considerations should be given for 24-hour prophylaxis against ischemia.
- If patients are intolerant to β-blocker therapy, consideration may be given to a CCB or a long-acting nitrate. Sinus node inhibition may be considered.
- If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. If combination β-blocker and CCB therapy is insufficient, a long-acting nitrate may be substituted for the CCB.

Treatment of Syndrome X

- Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination.
- Statin therapy is recommended for patients with dyslipidemia.
- ACE inhibitors are recommended in patients with hypertension.
- If pain persists despite the treatment recommendations given above, imipramine and aminophylline may be considered.

Treatment of Vasospastic/Variant Angina

- Treatment with CCBs is recommended. Nitrates may also be used if needed.

European Society of Cardiology (ESC): Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS) (2007)[9]

- β-blockers are recommended in most patients (in the absence of contraindications), especially in patients with hypertension or tachycardia.
- Oral or intravenous (IV) nitrates are recommended to relieve symptoms and in the acute management of anginal episodes.
- CCBs may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina.
- Non dihydropyridine CCBs should not be used unless combined with β-blockers.
- Anticoagulation and antiplatelet agents are recommended in all patients with ACS. The risk of both ischemic and bleeding events should be considered when choosing therapy.
- If an urgent, invasive strategy is to be used, unfractionated heparin (UFH), enoxaparin, or bivalirudin should be used immediately.
- In a non-urgent situation, fondaparinux is recommended as a first-line anticoagulant. Enoxaparin may be used instead only if the bleeding risk is low.
- During a percutaneous intervention (PCI), the initial anticoagulant should be continued. Additional UFH in the form of a bolus is recommended if fondaparinux is used.
- Anticoagulation may be stopped 24 hours after a PCI, or may be continued up to hospital discharge.
- Aspirin is recommended in all patients without contraindications at an initial dose of 160-325 mg followed by a maintenance dose of 75-100 mg indefinitely.
- A loading dose of clopidogrel is recommended for all patients followed by 75 mg daily for up to 12 months unless the patient is at a high risk of bleeding. Patients undergoing an invasive procedure/PCI may receive an initial loading dose of 600 mg of clopidogrel.
- Clopidogrel may be given to patients who are intolerant to aspirin therapy.
- For patients who are at intermediate-to-high risk (especially those with elevated troponin, ST-depression, or diabetes), eptifibatide or tirofiban is recommended in addition to antiplatelet agents.
- Consideration should be given to the risk of bleeding events.
- Patients receiving initial treatment with eptifibatide or tirofiban prior to angiography should be maintained on the same drug during and after PCI.
- Patients who are to undergo PCI who were not treated with a GP (glycoprotein) IIb/IIIa inhibitor, abciximab is recommended immediately after angiography.
- GP IIb/IIIa inhibitors must be combined with an anticoagulant.
- Bivalirudin may be used instead of GP IIb/IIIa inhibitors.

- When PCI is planned to be performed within 24 hours, data most strongly supports the use of abciximab.
- NSAIDs should not be administered with aspirin or clopidogrel.
- Clopidogrel may be administered with all statins.
- Interruption of dual antiplatelet therapy with aspirin and clopidogrel during the first 12 months after an event is not recommended unless severe, life-threatening bleeding occurs, or surgery is to be performed during which minor bleeding may result in serious consequences.
- Statins are recommended in all ACS patients regardless of cholesterol levels.
- Intensive lipid-lowering therapies (to an LDL-C goal of <70 mg/dL) are recommended.
- β-blockers should be initiated in all patients with left ventricular dysfunction.
- ACE inhibitors are recommended in all patients with left ventricular ejection fraction ≤ 40% and in patients with diabetes, chronic kidney disease, and hypertension unless otherwise contraindicated.
- ACE inhibitors should be considered for all other patients to prevent the recurrence of ischemia. Agents and doses of proven efficacy are recommended (ramipril and perindopril).
- ARBs should be considered in patients intolerant to ACE inhibitors and/or who have heart failure or have had an MI with a left ventricular ejection fraction of ≤ 40%.
- Aldosterone antagonists should be considered in patients who are already on an ACE inhibitor and β-blocker after an MI, who have a left ventricular ejection fraction of ≤ 40%, diabetes, or heart failure and who do not have significant renal dysfunction or hyperkalemia.

American College of Physicians (ACP): Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease (2004)[10]

Symptomatic Patients

- The following agents are recommended to prevent MI or death and to reduce symptoms: aspirin (clopidogrel may be used in patients intolerant to aspirin), β-blockers, statins, and ACE inhibitors.
- The following agents are recommended to reduce symptoms only: NTG (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when monotherapy has been unsuccessful.
- The following agents are not recommended to prevent MI or death or to reduce symptoms: dipyridamole and chelation therapy.

Asymptomatic Patients With Evidence Suggesting CAD on Previous Testing

- The following agents should be used to prevent MI and death: aspirin (in patients with a previous MI), β-blockers (in patients with a previous MI), statins (in patients with type 2 diabetes or documented CAD), and an ACE inhibitor (in patients with documented CAD and diabetes, systolic dysfunction, or both).
- The following agents may also be used to prevent MI and death: aspirin in patients who have not had a previous MI, and an ACE inhibitor in patients with diabetes and no contraindications.

Blood pressure is reported as mm Hg with the first number being systolic pressure and second number being diastolic pressure.

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Appendix
Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Chronic Heart Failure
September 10, 2008

I. Overview

Approximately 5 million people in the United States have heart failure.[1] The incidence of heart failure is approximately 10 per 1,000 individuals after the age of 65 years and roughly 80% of patients who are hospitalized for heart failure are over 65.[1] Although heart failure is a progressive disease, appropriate and timely treatment may slow or halt the progression of the disease, and ventricular remodeling may improve.[2]

The term heart failure refers to a syndrome caused by cardiac dysfunction typically resulting from myocardial muscle dysfunction and associated left ventricular dilation or hypertrophy. It is characterized by elevated cardiac filling pressure and/or inadequate peripheral oxygen delivery, both of which are the result of cardiac dysfunction.[2] Symptoms of heart failure include fluid retention, shortness of breath, and fatigue.[2] The presence and severity of clinical symptoms does not always correlate with the degree of cardiac function. Most patients with heart failure have evidence of left ventricular systolic dysfunction, with or without accompanying diastolic dysfunction.[3] Diastolic heart failure often occurs in the presence of preserved resting left ventricular ejection fraction and is uncommon in younger patients.[3] The most common system used to classify heart failure was developed by the New York Heart Association (NYHA) and places patients in one of 4 functional classes. Additionally, the American College of Cardiology (ACC) and the American Heart Association (AHA) created stages to describe the progression of heart failure and these stages serve to complement the NYHA functional classes.[1,4] The NYHA and ACC/AHA classifications and staging symptoms are described in Tables 1 and 2.

Table 1. NYHA Classification of Heart Failure[1,4]

NYHA Functional Class	
Class	**Description**
I (Mild)	No limitation of physical activity; ordinary exertion does not cause symptoms.
II (Mild)	Symptoms with ordinary exertion but comfortable at rest.
III (Moderate)	Marked limitation of physical activity; less than ordinary activity causes symptoms but comfortable at rest.
IV (Severe)	Symptoms of heart failure at rest.

Table 2. ACC/AHA Classification of Heart Failure[1,4]

ACC/AHA Stage	
Stage	**Description**
A	At high risk of developing heart failure due to predisposing conditions, no structural abnormalities or symptoms of heart failure.
B	Structural heart disease but no signs or symptoms of heart failure.
C	Current or prior symptoms of heart failure and structural heart disease.
D	Advanced structural heart disease and heart failure symptoms at rest; requires specialized intervention.

II. Evidence-Based Medicine and Current Treatment Guidelines

Table 3. Current Treatment Guidelines for Chronic Heart Failure

American College of Cardiology (ACC)/American Heart Association (AHA): Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)[1]
Patients at Risk for Developing Heart Failure (Stage A)

- Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy.
- Lipid disorders should be treated according to contemporary guidelines.
- Blood sugar in patients with diabetes should be controlled according to contemporary guidelines. ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, myocardial infarction (MI), and heart failure. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left ventricular dysfunction or hypertension.
- Patients with known atherosclerotic vascular disease should be treated according to current guidelines for secondary prevention.
- ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes, and hypertension with other cardiovascular risk factors.

<u>Patients With Cardiac Structural Abnormalities or Remodeling Who Have not Developed Heart Failure Symptoms (Stage B)</u>

- β-Blockers and ACE inhibitors should be used in all patients with a recent or past history of MI.
- β-Blockers and ACE inhibitors should be used in patients who have reduced left ventricular ejection fraction and do not have a history of MI or heart failure.
- ARBs are recommended for patients with reduced left ventricular ejection fraction and a history of an MI if they are intolerant to ACE inhibitors.
- ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy.
- Digoxin is not recommended in patients with a low ejection fraction, no heart failure symptoms, and sinus rhythm.
- Calcium-channel blocking agents (CCBs) with negative inotropic effects are not recommended in asymptomatic patients with low ejection fraction after an MI.

<u>Patients With Current or Prior Symptoms of Heart Failure (Stage C)</u>

- Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention.
- ACE inhibitors are recommended in all patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated.
- β-Blockers (bisoprolol, carvedilol, or extended-release metoprolol) are recommended in all stable patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated.
- ARBs approved for the treatment of heart failure are recommended in all patients intolerant to ACE inhibitors with current or past symptoms of heart failure and reduced left ventricular ejection fraction.
- Drugs known to adversely affect patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction (nonsteroidal anti-inflammatory drugs (NSAIDs), some CCBs, some antiarrhythmic medications) should be discontinued and avoided if possible.
- Aldosterone antagonists may be beneficial in patients with moderately severe-to-severe symptoms of heart failure with reduced left ventricular ejection fraction, though careful monitoring is required.
- ARBs are reasonable alternatives to ACE inhibitors as first-line therapy in patients with mild-to-moderate heart failure and reduced left ventricular ejection fraction.
- Digoxin may be beneficial in decreasing hospitalizations in patients with current or past history of heart failure and reduced left ventricular ejection fraction.
- The addition of a nitrate and hydralazine is reasonable in patients with reduced left ventricular ejection fraction already on an ACE inhibitor and β-blocker and who have persistent symptoms.
- The combination of a nitrate and hydralazine is reasonable in patients who are intolerant to ACE inhibitor and ARB therapy or in whom therapy with one of these agents is contraindicated.
- The addition of an ARB is reasonable in patients who are symptomatic despite conventional treatment.
- The routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended.
- CCBs are not recommended as routine treatment for heart failure.

Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

- Systolic and diastolic hypertension should be controlled according to contemporary guidelines.
- Ventricular rate should be controlled in patients with atrial fibrillation.
- Diuretics are recommended to control pulmonary congestion and peripheral edema.
- Restoration and maintenance of normal sinus rhythm may be beneficial in patients with atrial fibrillation and heart failure to control symptoms.
- β-Blockers, ARBs, ACE inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms.
- The role of digoxin in patients with heart failure and preserved left ventricular ejection fraction is not well established.

Patients With Refractory End-Stage Heart Failure (Stage D)

- Treatment of fluid retention is important.
- Continuous infusion of a positive inotropic agent may be considered for palliative care.

Special Populations

- Hydralazine and isosorbide dinitrate may be beneficial when added to the standard treatment including β-blockers and ACE inhibitors in African American patients with New York Heart Association (NYHA) functional class III or IV.

Patients with Concomitant Disorders

- All recommendations should apply to patients with concomitant disorders unless exceptions exist.
- Nitrates and β-blockers are recommended in patients with heart failure and angina.
- Anticoagulants are recommended in patients with heart failure and atrial fibrillation or a previous thromboembolic event.
- In patients with atrial fibrillation, ventricular response rate should be controlled with a β-blocker or amiodarone (if a β-blocker is not tolerated).
- Patients with underlying coronary artery disease (CAD) should be prescribed antiplatelet agents.
- Digoxin is reasonable to control ventricular rate in patients with atrial fibrillation and heart failure.
- Amiodarone is a reasonable option to decrease the recurrence of atrial arrhythmias.
- The benefit of enhancing erythropoiesis in patients with heart failure and anemia is not established.
- Class I or II antiarrhythmics are not recommended in patients with heart failure for the prevention of ventricular arrhythmias.
- Antiarrhythmics are not recommended to treat asymptomatic ventricular arrhythmias.

Heart Failure Society of America (HFSA): 2006 Comprehensive Heart Failure Practice Guideline (2006)[2]

- ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria.
- β-Blockers are recommended in patients who have had an MI to reduce mortality, recurrent MI, and prevent heart failure.
- Pneumococcal and influenza vaccines are recommended in all patients unless otherwise contraindicated.
- NSAIDs, including cyclooxygenase (COX)-2 inhibitors should be avoided.

Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction

- ACE inhibitors are recommended. ARBs may be used in patients who are intolerant to ACE inhibitors.
- Routine use of ACE inhibitors and ARBs together is not recommended.
- β-Blocker therapy is recommended.

Patients With Left Ventricular Systolic Dysfunction

- ACE inhibitors should be used in all patients with a left ventricular ejection fraction ≤ 40% unless otherwise contraindicated.
- ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated.

- β-Blockers should be used in all patients with a left ventricular ejection fraction ≤ 40%, unless otherwise contraindicated.
- The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a left ventricular ejection fraction ≤ 40%.
- β-Blocker therapy is recommended in patients with recent decompensation of heart failure after stabilization and discontinuation of intravenous (IV) vasoactive agents and diuretics.
- β-Blockers are recommended regardless of the presence of diabetes, chronic obstructive lung disease, or peripheral vascular disease, though caution is recommended in patients with diabetes with recurrent hypoglycemia, asthma, or resting limb ischemia. Considerable caution is recommended in patients with marked bradycardia (<55 beats per minute) or hypotension (systolic blood pressure <80 mm Hg).
- β-Blockers are not recommended in patients with asthma with active bronchospasm.
- It is recommended that the dose of β-blocker therapy be titrated slowly. Therapy should continue in most cases during symptomatic exacerbations, though the dose may need to be decreased.
- The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had an MI and have left ventricular dysfunction is not recommended.
- Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had an MI and in patients with chronic heart failure and systolic dysfunction.
- An aldosterone antagonist may be added to the standard medication regimen (including diuretics) in patients who are in NYHA functional class IV or those in class III previously in class IV (left ventricular ejection fraction ≤35%) from left ventricular systolic dysfunction.
- An aldosterone antagonist should be considered in patients who have had an MI and who have symptomatic heart failure and left ventricular ejection fraction ≤ 40% while receiving standard therapy with an ACE inhibitor (or ARB) and a β-blocker.
- A combination of hydralazine and an oral nitrate is recommended in African American patients who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker.
- A combination of hydralazine and an oral nitrate may be considered in non–African American patients who are symptomatic despite optimization of standard therapy.
- Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics are typically preferred.
- Torsemide may be considered in patients in whom erratic diuretic effect or absorption is present.
- Metolazone or chlorothiazide may be given to patients with persistent fluid retention despite high dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion.
- Digoxin may be considered in patients with left ventricular ejection fraction ≤ 40% who have symptomatic heart failure despite therapy with ACE inhibitors and β-blockers.
- High doses of digoxin for rate control are not recommended.
- Warfarin is recommended for all patients with heart failure and atrial fibrillation or history of systemic or pulmonary emboli.
- Patients with symptomatic or asymptomatic ischemic cardiomyopathy and recent large anterior MI or a history of a MI with left ventricular thrombus should be treated with warfarin for 3 months following the MI.
- Warfarin should be considered in patients with dilated cardiomyopathy and left ventricular ejection fraction ≤ 35%.
- Long-term antithrombotic treatment is recommended in patients with heart failure due to ischemic cardiomyopathy regardless of ACE inhibitor use. Aspirin (75 mg or 81 mg) is recommended in patients who do not have a specific indication for anticoagulation. Warfarin and clopidogrel may be considered as alternatives to aspirin.
- Aspirin is not recommended routinely in patients with heart failure which is not due to ischemic cardiomyopathy and who do not have other atherosclerotic vascular disease.
- The combination of an ACE inhibitor and aspirin may be considered in patients who have indications for both medications.
- Antiarrhythmics (including amiodarone) are not recommended as primary prophylaxis for sudden death in patients with heart failure.

<u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u>

- Diuretics are recommended in patients with evidence of fluid overload.
- ACE inhibitors or ARBs should be considered in this patient population.

- ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease (CVD) or diabetes and at least 1 other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors.
- β-blockers are recommended in patients with heart failure and preserved left ventricular ejection fraction who have also had an MI, hypertension, or atrial fibrillation requiring ventricular rate control.
- CCBs should be considered in patients who have hypertension (amlodipine should be considered) or angina, and in those who have atrial fibrillation requiring ventricular rate control and are intolerant to β-blockers.

Patients With Acute Decompensated Heart Failure

- IV vasodilators, diuretics, and inotropes have all been used to treat patients with acute decompensated heart failure.

Patients With Heart Failure and Coronary Artery Disease

- Antiplatelet therapy is recommended.
- ACE inhibitors are recommended after an MI.
- β-blockers are recommended in patients with reduced left ventricular ejection fraction and in patients who have had an MI.
- ACE inhibitor and β-blocker therapy should be initiated early (within <48 hours) in hospitalized stable patients who have had an MI and have left ventricular dysfunction.
- Nitrates may be considered in patients who need additional management for symptomatic angina.
- CCBs should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function.

Managing Patients With Heart Failure and Hypertension

- Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic, and a β-blocker or CCB.
- Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a CCB or other antihypertensive agent.
- Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists, and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing CCB (amlodipine) may be considered.

Managing Heart Failure in the Elderly, Women, and African Americans

- Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure.
- ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction.
- ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors.
- Hydralazine and isosorbide dinitrate are recommended in all African American patients (in addition to standard therapy with ACE inhibitors and β-blockers) with left ventricular systolic dysfunction who are in NYHA classes II-IV.

European Society of Cardiology (ESC): Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (2005)[3]

- ACE inhibitors are recommended in patients with left ventricular ejection fraction 40%-45% with or without symptoms. Doses should be titrated to those found effective in clinical trials (and not based on symptomatic improvement alone). Diuretics should be added if there is evidence of fluid retention.
- ARBs may be used in patients who are intolerant to ACE inhibitor therapy. They may also be used in combination with ACE inhibitors in patients who remain symptomatic.
- Diuretics are recommended for the symptomatic treatment of heart failure when pulmonary congestion or peripheral

edema is present. They should be combined with an ACE inhibitor and β-blocker if tolerated.

- Potassium-sparing diuretics are only recommended if hypokalemia persists despite ACE inhibition or in patients with severe heart failure who are already on a combination of an ACE inhibitor and low-dose spironolactone, or in patients who are intolerant to even low doses of spironolactone.
- β-blockers are recommended in all patients with heart failure. Carvedilol, metoprolol succinate, and bisoprolol are the recommended β-blocking agents. Small initial doses are recommended, titrating upward as tolerated.
- Aldosterone antagonists are recommended in addition to ACE inhibitors, β-blockers, and diuretics in patients who have advanced heart failure (NYHA class III-IV) with systolic dysfunction, and in patients who are unable to tolerate therapy with ACE inhibitors.
- Aldosterone antagonists are recommended in combination with an ACE inhibitor and a β-blocker in patients who have had an MI and who have left ventricular systolic dysfunction and signs of heart failure.
- A combination of digoxin and a β-blocker seems to be more efficacious to either agent alone in patients with atrial fibrillation. Digoxin may reduce hospitalizations in patients with heart failure caused by left ventricular systolic dysfunction and sinus rhythm who are already treated with ACE inhibitors, β-blockers, diuretics, and spironolactone (in severe heart failure).
- A combination of hydralazine and isosorbide dinitrate may be tried in patients who are intolerant to ACE inhibitors and ARBs.
- Nitrates may be considered in patients with co morbid angina.
- There is no evidence to support the use of α-adrenergic blocking agents (α-blockers) in heart failure.
- The CCBs diltiazem and verapamil are not recommended in patients with heart failure caused by systolic dysfunction. The addition of felodipine or amlodipine does not improve survival or symptoms, though may be helpful in patients with angina or arterial hypertension not controlled with nitrates and β-blockers.
- Clinical experience with nesiritide in patients with acute heart failure is limited.
- Anticoagulation is indicated in patients with heart failure from atrial fibrillation and a previous thromboembolic event or a mobile left ventricular thrombus.
- Aspirin or oral anticoagulants are recommended in patients with heart failure who have had a previous MI.
- Aspirin should be avoided in patients with recurrent hospitalization due to worsening heart failure.
- Antiarrhythmic therapy may be indicated in patients with heart failure and atrial fibrillation or ventricular tachycardia. Class I antiarrhythmics should be avoided. β-blockers may be used alone or in combination with amiodarone in patients with ventricular tachyarrhythmias. Amiodarone may be used in patients with ventricular and supraventricular tachyarrhythmias. It is preferred in patients with heart failure and atrial fibrillation and may improve the success of electrical cardioversion. Routine administration of amiodarone is not recommended.
- High doses of ARBs may reduce hospitalizations in patients with heart failure and preserved left ventricular ejection fraction or diastolic dysfunction.

Blood pressure is reported as mm Hg with the first number being systolic pressure and second number being diastolic pressure.

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Appendix
Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Hypertension
September 10, 2008

I. Overview

Hypertension, or persistent elevation of arterial blood pressure, affects approximately 73 million people in the United States (US), or one-third of adults.[1,2] Primary or essential hypertension has an unknown identifiable etiology and accounts for over 90%, and perhaps as many as 95%, of all cases.[3,4] Hypertension due to a specific cause, known as secondary hypertension, accounts for the remaining cases. The most common causes for secondary hypertension are renal parenchymal disease (2%-5% of cases) and renal artery stenosis (1%-2%).[4,5] Hypertension may also be the result of primary hyperaldosteronism, Cushing's syndrome, pheochromocytoma, coarctation of the aorta, pregnancy, estrogen use, or other causes.[4]

The prevalence of hypertension increases with age. Approximately 64% of American men aged 65-74 years have hypertension, and 69% of those aged 75 years and older have hypertension.[1,2] For women in the same age brackets the figures are higher, with rates of 74% and 84%.[1,2] The prevalence of hypertension in African American patients is among the highest in the world. In 2002, the prevalence of hypertension in African American adults was 41.4% African American patients tend to develop hypertension earlier in life and average blood pressure is higher compared to white patients.[1] A diagnosis of hypertension is made based upon the average of two or more properly measured systolic and diastolic blood pressure readings that are greater than 140 mm Hg or 90 mm Hg, respectively. The classification of blood pressure in adults according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) is provided in Table 1.[6] Though this classification system is commonly used and referenced, other guidelines included in this review may classify hypertension by other methods. Where applicable, these classification systems are included in the discussion of the guidelines in which they are presented.

Table 1. JNC 7 Classification of Blood Pressure for Adults Aged 18 Years or Older[6]

Blood Pressure Classification	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	<120 (mm Hg)	and	<80 (mm Hg)
Prehypertension	120-139 (mm Hg)	or	80-89 (mm Hg)
Stage 1 hypertension	140-159 (mm Hg)	or	90-99(mm Hg)
Stage 2 hypertension	≥ 160 (mm Hg)	or	≥ 100 (mm Hg)

Most patients with mild-to-moderate hypertension are asymptomatic.[7] Over time, chronic hypertension can lead to complications such as cardiovascular morbidity and mortality. Hypertension often coexists with other major cardiovascular risk factors that affect prognosis. These risk factors include cigarette smoking, obesity, physical inactivity, dyslipidemia, diabetes, microalbuminuria, estimated glomerular filtration rate <60 milliliters per minute, age >55 years for men or >65 years for women, and family history of premature cardiovascular disease (CVD).[6]

Uncontrolled hypertension can also progress to end-organ damage involving changes in the eye, brain, heart, kidneys, and peripheral blood vessels.[5] Therefore, it is imperative to treat hypertension. Antihypertensive therapy has been shown to reduce the incidence of stroke by 35%-40%, myocardial infarction (MI) by 20%-25%, and heart failure by more than 50%.[6]

II. Evidence-Based Medicine and Current Treatment Guidelines

Current guidelines for the treatment of hypertension are outlined in Table 2. In the US, the JNC 7 is the most widely utilized guideline for the management of hypertension.[6] There are also other important national and international hypertension guidelines.[8-12] In addition, various groups of specialists have developed their own guidelines for specific patient populations.[13-15]

In 2006, the British Hypertension Society (BHS) and the National Institute for Clinical Excellence (NICE) collaborated to update their recommendations for the pharmacologic treatment of hypertension.[11] This 2006 update replaces the pharmacologic recommendations in the previously published NICE guidelines for hypertension (2004).[16] The previous hypertension guideline from the BHS, also published in 2004 and known as the BHS IV, contains some nonpharmacologic recommendations and blood pressure goals that were not superseded by the BHS/NICE 2006 update.[12] Therefore, a discussion of these recommendations from the BHS IV is also included below.

Table 2. Current Treatment Guidelines for Hypertension

National Heart, Lung, and Blood Institute (NHLBI): The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)[6]
• In patients older than 50 years, systolic blood pressure is a more important determinant of cardiovascular disease (CVD) risk than diastolic blood pressure. • The risk of CVD begins to rise at blood pressures above 115/75 mm Hg and doubles for each incremental increase of 20/10 mm Hg in blood pressure. • Lifestyle modifications including diet, exercise, alcohol restriction, and weight reduction are recommended in pre-hypertensive patients with systolic blood pressure of 120-139 mm Hg or diastolic blood pressure of 80-89 mm Hg. • Drug therapy is typically initiated when systolic pressure is ≥140 mm Hg and/or diastolic pressure is ≥ 90 mm Hg. In patients with diabetes, proteinuric chronic renal failure, or CVD, drug therapy is indicated when systolic pressure is persistently ≥ 130 mm Hg and/or diastolic pressure is ≥80 mm Hg. • Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-adrenergic blocking agents (β-blockers), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium-channel blocking agents (CCBs). This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting CCBs may also be used. • In patients with acute coronary syndromes (ACS) (MI or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. Other medications may be used as needed for blood pressure control. • For patients with post-MI, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria.

- Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications.
- African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE-inhibitor-induced angioedema is 2-4 times higher in African American patients.
- Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators.
- Thiazide diuretics are useful in slowing demineralization in osteoporosis.
- β-Blockers are useful in the treatment and/or prophylaxis of atrial arrhythmias/fibrillation, migraine, thyrotoxicosis (short term), essential tremor, and perioperative hypertension.
- CCBs may be useful in Raynaud's syndrome and certain arrhythmias.
- α-Adrenergic blocking agents (α-blockers) may be useful in prostatism.
- Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
- β-Blockers should be used cautiously or avoided in patients with asthma, reactive airways disease, or second or third degree heart block.
- ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
- ACE inhibitors should not be used in patients who have a history of angioedema.
- Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should not be used in patients whose potassium levels are greater than 5.0 mEq/L.

World Health Organization (WHO)/International Society of Hypertension (ISH): 2003 WHO/ISH Statement on Management of Hypertension (2003)[8]

- Target blood pressure goal is <140/90 mm Hg for low-risk patients with uncomplicated hypertension and <130/80 mm Hg for high-risk patients (eg, patients with established CVD, diabetes, renal insufficiency).
- A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class.
- If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents.
- When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients.
- α-Blockers may be useful in patients with prostatism.
- Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).

European Society of Hypertension (EHS)/European Society of Cardiology (ESC): 2007 Guidelines for the Management of Hypertension (2007)[9]

- Blood pressure is categorized as follows: (<120 and <80 mm Hg), normal (120-129 and/or 80-84 mm Hg), high normal (130-139 and/or 85-89 mm Hg), grade I hypertension (140-159 and/or 90-99 mm Hg), grade II hypertension (160-179 and/or 100-109 mm Hg), grade III hypertension (≥ 180 and/or ≥ 110 mm Hg), and isolated systolic hypertension (≥ 140 and <90 mm Hg).
- Initiation of drug therapy should be based on blood pressure and total cardiovascular risk.
- The blood pressure goal is <140/90 mm Hg for all hypertensive patients. The goal of treatment for a diabetic patient is blood pressure of <130/80 mm Hg.
- The choice of drug should depend on several factors, including previous patient response to a class of medications, the

effect of a medication on cardiovascular risk according to the patient's cardiovascular profile, presence of compelling indications for certain medications, the presence of disorders which may limit the use of a class of medications, possibility of drug interactions, and side effects.

- Drugs which exert their effects for 24 hours and can be given once daily should be preferred to enhance compliance.
- There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, non dihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics).
- Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk.
- Fixed combination medications can favor compliance and simplify regimens.
- When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated.
- Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers.
- CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
- Lipid-lowering therapy, antiplatelet therapy, and glycemic control are recommended in appropriate patients.

Treatment Guidelines From the Medical Letter on Drugs and Therapeutics: Drugs for Hypertension (2005)[10]

- Initial drugs of choice include: a thiazide diuretic for many patients; ACE inhibitor or ARBs for patients with left ventricular dysfunction, heart failure, or diabetic nephropathy; β-blockers for patients with angina pectoris or migraine headaches and for some patients with heart failure; a diuretic or a dihydropyridine CCB for older patients with isolated systolic hypertension; and a diuretic or CCB for African American patients.
- Many patients (about 40%) need more than one drug to achieve blood pressure control. A diuretic is recommended as the drug of choice for add-on therapy if it has not been used initially. Patients with severe hypertension may need two drugs at the onset of treatment.

National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)[11]

- Drug therapy should be offered to patients with persistent high blood pressure of ≥ 160/100 mm Hg or those with persistent high blood pressure of >140/90 mm Hg and at high cardiovascular risk (10-year risk of CVD of ≥20% or existing CVD or target organ damage).
- Target blood pressure goal is <140/90 mm Hg.
- Patients with isolated systolic hypertension should be offered the same treatment options as patients with elevated systolic and diastolic blood pressure.
- Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic.
- Initial therapy in patients younger than 55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors.
- If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added.
- If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.
- If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker.

- β-blockers are generally not preferred for initial therapy for hypertension, though they may be used in younger patients in the case of ACE inhibitor and ARB intolerance, in women of childbearing age, and in patients with an increased sympathetic drive.
- If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes).
- Patients who are well-controlled on a β-blocker do not need to be switched from the β-blocker to an alternative agent.
- If a β-blocker is to be discontinued, the dose should be gradually decreased. β-blockers should not be discontinued in patients who have a compelling indication for β-blockade, including those with angina and those who have had an MI.

British Hypertension Society (BHS): Guidelines for Hypertension Management 2004 (BHS-IV)[12]

- Blood pressure is categorized as follows: optimal (<120 and <80 mm Hg), normal (<130 and <85 mm Hg), high normal (130-139 and/or 85-89 mm Hg), grade I hypertension (140-159 and/or 90-99 mm Hg), grade II hypertension (160-179 and/or 100-109 mm Hg), grade III hypertension (≥ 180 and/or ≥ 110 mm Hg), and isolated systolic hypertension (grade I: ≥ 140 and <90 mm Hg, grade II: ≥ 160 and <90 mm Hg).
- For patients with CVD, other end-organ damage, diabetes mellitus, or an estimated CVD risk of ≥ 20% over 10 years, drug therapy is recommended when systolic blood pressure is 140-159 mm Hg, diastolic blood pressure is 90-99 mm Hg, or both. Otherwise, drug therapy is recommended when blood pressure is ≥ 160/100 mm Hg.
- A target blood pressure goal of ≤ 140/85 mm Hg is recommended for nondiabetic patients and ≤ 130/80 mm Hg for patients with diabetes, renal impairment or established CVD.

American Diabetes Association (ADA): Standards of Medical Care in Diabetes—2008[13]

- The blood pressure goal is <130/80 mm Hg for patients with diabetes.
- Patients with systolic blood pressure readings of 130-139 mm Hg or diastolic readings of 80-89 mm Hg should be treated for 3 months with lifestyle modifications. If goal is not achieved in 3 months, pharmacologic treatment is indicated.
- Patients with systolic blood pressure readings of ≥ 140 mm Hg or diastolic readings of ≥ 90 mm Hg should be treated with pharmacologic interventions in addition to lifestyle modifications.
- The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥ 50 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <50 mL/min/1.73 m^2.
- Multiple drug therapy is generally required to achieve blood pressure goals.

International Society on Hypertension in African Americans: Management of High Blood Pressure in African Americans (2003)[14]

- Blood pressure goals are <140/90 mm Hg for patients with uncomplicated essential hypertension and <130/80 mm Hg for patients with diabetes, nondiabetic renal disease with significant proteinuria, history of cardiovascular event or stroke, or high risk for coronary artery disease.
- All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required.
- ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy.
- CCBs and thiazide diuretics may be more effective than other drug classes in African Americans.
- In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients.
- African American patients appear to be at an increased risk for ACE inhibitor-associated cough, angioedema, or both.

Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.

National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)[15]
• Patients with chronic kidney disease should be considered in the "highest risk" group for CVD and should be treated accordingly. • Target blood pressure goal should be <130/80 mm Hg. • All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, non dihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥ 200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥ 30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence. • Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible.

Blood pressure is reported as mm Hg with the first number being systolic pressure and second number being diastolic pressure.

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