Therapeutic Class Overview
Angiotensin-Converting Enzyme (ACE) Inhibitors

INTRODUCTION

- Approximately 121.5 million American adults are living with some form of cardiovascular (CV) disease or the after-effects of stroke, according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2019 update *(Benjamin et al 2019).* CV disease is the number one cause of death in the United States.
- Hypertension (HTN) is an independent risk factor for CV disease and increases the mortality risks of CV disease and other diseases *(Benjamin et al 2019).* The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as blood pressure (BP) ≥ 130/80 mm Hg (*Whelton et al 2018).* Nearly half of American adults (46%) have HTN based on this definition.
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal CV events including stroke and myocardial infarctions (MIs). Lipid control, diabetes mellitus (DM) management, smoking cessation, exercise, weight management, and limiting sodium intake may also reduce CV risk *(Benjamin et al 2019).*
- Numerous classes of antihypertensives are available to reduce BP. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta (β)-blockers, and calcium channel blockers (CCBs). Selection of antihypertensive therapy for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as heart failure (HF), DM, chronic kidney disease (CKD), history of stroke or MI, and risk factors for coronary heart disease (CHD). Some patients require 2 or more antihypertensives from different pharmacological classes to achieve BP control *(Go et al 2014, Weber et al 2014, Whelton et al 2018).*
- In general, guideline-recommended BP goals in hypertensive adults range from < 130/80 mm Hg to < 140/90 mm Hg *(American Diabetes Association 2019, de Boer et al 2017, Whelton et al 2018).*
  - BP goals for older patients have long been a point of debate. The SPRINT trial followed patients ≥ 50 years with high BP and increased CV risks under intense hypertensive treatment (systolic blood pressure [SBP] goal of < 120 mm Hg) compared to standard HTN treatment (SBP goal of < 140 mm Hg) over a period of 3.2 years. The trial ended early; however, results demonstrated a reduced primary composite outcome of MI, acute coronary syndrome (ACS), stroke, HF, or CV death driven mainly by reduced HF events and CV death with intense treatment compared to standard treatment. The SPRINT trial pointed to potential clinical benefits associated with more intensive treatment in certain patients, although early termination of the trial and variations in the BP-measurement technique employed have called into question the generalizability of the results *(SPRINT Research Group 2015).*
  - A guideline from the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) on treatment of HTN in adults aged ≥ 60 years recommends standard and intense SBP treatment goals of < 150 mm Hg and < 140 mm Hg, respectively, with more intense BP reduction reserved for patients with a history of stroke or transient ischemic attack *(Qaseem et al 2017).*
- This review includes the ACE-Is and the ACE-I combination products.
  - The ACE-Is are Food and Drug Administration (FDA)-approved to treat HTN, HF, left ventricular (LV) dysfunction, diabetic nephropathy, acute myocardial infarction (AMI) to improve survival, and stable coronary artery disease (CAD) to reduce the risk of CV mortality or nonfatal MI.
  - The ACE-I combinations are products that combine an ACE-I with the diuretic hydrochlorothiazide (HCTZ), or a CCB (amlodipine or verapamil) in a fixed-dose formulation. 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. All of the combination ACE-Is are FDA-approved for the treatment of HTN; however, with the exceptions of captopril/HCTZ and perindopril/amlodipine, none are FDA-approved for initial treatment of HTN.
- The single entity and combination ACE-Is included in this review are listed in Table 1.
- Medispan class: Antihypertensives - ACE Inhibitors; ACE Inhibitors & Thiazide/Thiazide-Like; ACE Inhibitor & Calcium Channel Blocker Combinations

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Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity ACE-Inhibitors	
Accupril (quinapril)	✔
Altace (ramipril)	✔
captopril*	✔
enalaprilat*	✔
fosinopril*	✔
Lotensin (benazepril)	✔
moexipril*	✔
perindopril*	✔
Prinivil, Qbrelis, Zestril (lisinopril)	✔ (Prinivil and Zestril only)
trandolapril*	✔
Vasotec, Epaned (enalapril)	✔ (Vasotec only)
ACE-I/HCTZ Combinations	
Accuretic (quinapril/HCTZ)	✔
captopril/HCTZ*	✔
fosinopril/HCTZ*	✔
Lotensin HCT (benazepril/HCTZ)	✔
moexipril/HCTZ*	✔
Vaseretic (enalapril/HCTZ)	✔
Zestoretic (lisinopril/HCTZ)†	✔
ACE-I/CCB Combinations	
Lotrel (benazepril/amlodipine)	✔
Prestalia (perindopril/amlodipine)	-
Tarka (trandolapril/verapamil ER)	✔

*Branded Aceon (perindopril), Capoten (captopril), Monopril (fosinopril), Univasc (moexipril), Vasotec (enalaprilat), Mavik (trandolapril), Capozide (captopril/HCTZ), Monopril HCT (fosinopril/HCTZ), and Uniretic (moexipril/HCTZ) are no longer marketed.

†Branded Prinzide (lisinopril/HCTZ) is no longer marketed; however, branded Zestoretic and generic products are available.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. FDA-Approved Indications for Single-Entity ACE-Is

Indication	benazepril	captopril	enalapril/ enalaprilat	Epaned (enalapril)	fosinopril	lisinopril	moexipril	perindopril	Qbrelis (lisinopril)	quinapril	ramipril	trandolapril
Acute MI to improve survival						✔			✔			
Asymptomatic left ventricular dysfunction			✔ †	✔ §								
Diabetic nephropathy		✔										
Heart failure		✔	✔ †	✔ ‡	✔	✔			✔	✔	✔ *	✔ *
Hypertension in adults	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypertension in children aged > 1 month			✔ †	✔ **								
Hypertension in children aged ≥ 6 years	✔				✔	✔			✔			
Left ventricular dysfunction after MI		✔										✔

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Indication	benazepril	captopril	enalapril/ enalaprilat	Epaned (enalapril)	fosinopril	lisinopril	moexipril	perindopril	Qbrelis (lisinopril)	quinapril	ramipril	trandolapril
Stable coronary artery disease to reduce the risk of CV mortality or nonfatal MI								✔				
Reduce risk of MI, stroke, and death from CV causes in patients ≥ 55 years of age at high risk for a major CV event											✔	

Abbrv: CV=cardiovascular, MI=myocardial infarction
*Post-MI
** Epaned is not recommended in neonates (ie, infants 1 month of age or less), preterm infants who have not reached a corrected post-conceptual age of 44 weeks, and in pediatric patients with glomerular filtration rate < 30 mL/min/1.73m^2.
†Enalapril oral tablets only
‡For symptomatic heart failure usually in combination with diuretics and digitalis.
§For clinically stable asymptomatic patients with ejection fraction ≤35%.

(Prescribing Information: Accupril 2017, Altace 2018, captopril 2019, enalaprilat 2018, Epaned 2018, fosinopril 2017, Lotensin 2019, moexipril 2015, perindopril 2019, Prinivil 2019, Qbrelis 2018, trandolapril 2018, Vasotec 2018, Zestril 2018)

Table 3. FDA-Approved Indications for Combination ACE-Is

Generic Name	Hypertension; not for initial therapy	Hypertension in patients not adequately controlled on monotherapy with either agent	Hypertension as either initial therapy or substituted for previously titrated doses of the individual products	Hypertension as either initial therapy or in patients not adequately controlled on monotherapy
ACE-I/HCTZ Combinations				
benazepril/HCTZ	✔			
captopril/HCTZ			✔	
enalapril/HCTZ	✔			
fosinopril/HCTZ	✔			
lisinopril/HCTZ	✔			
moexipril/HCTZ	✔			
quinapril/HCTZ	✔			
ACE-I/CCB Combinations				
benazepril/amlodipine		✔		
perindopril/amlodipine*				✔
trandolapril/verapamil ER	✔			

Abbrv: ACE=angiotensin converting enzyme, CCB=calcium channel blocker, ER=extended release, HCTZ=hydrochlorothiazide
*Perindopril/amlodipine may be used as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals.

(Prescribing Information: Accuretic 2017, captopril/HCTZ 2006, fosinopril/HCTZ 2018, Lotensin HCT 2018, Lotrel 2017, moexipril/HCTZ 2017, Prestalia 2019, Tarka 2019, Vaseretic 2017, Zestoretic 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- ACE-Is have demonstrated efficacy for the treatment of HTN in adults. A Cochrane systematic review of 92 randomized, placebo-controlled trials evaluated the BP-lowering ability of 14 different ACE-Is (N = 12,954). On average, SBP was

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lowered by 8 mm Hg and diastolic blood pressure (DBP) by 5 mm Hg. There were no clinically meaningful BP lowering differences among the various ACE-Is *(Heran et al 2008).*
  - Enalapril has demonstrated efficacy for the treatment of HTN in children aged 6 to 16 years *(Wells et al 2002).*
  - Meta-analyses have shown that ACE-Is and ARBs have similar long-term effects on BP *(Sanders et al 2011, Savarese et al 2013).* Additionally, a Cochrane review involving 11,007 subjects with primary HTN found no evidence of a difference in total mortality or CV outcomes for ACE-Is in comparison to ARBs (*Li 2014*).
- ACE-Is have been shown to be effective for CAD and in reducing the risk for CV mortality, MI, and stroke in clinical trials *(ADVANCE Collaborative Group 2007, Blood Pressure Lowering Treatment Trialists' Collaboration 2007, Dahlof et al 2005, Fox et al 2003, Nissen et al 2004, ONTARGET Investigators 2008, Pilote et al 2004, Pitt et al 2003, PREAMI Investigators 2006, PROGRESS Collaborative Group 2001, Sanders et al 2011, Savarese et al 2013, Swedberg et al 1992, The Heart Outcomes Prevention Evaluation Study Investigators 2000, The PEACE Trial Investigators 2004, van Vark et al 2012, Zoungas et al 2014).*
  - Additionally, in a retrospective analysis of patients > 65 years of age, ramipril was associated with significantly lower mortality 1 year after MI compared to captopril, enalapril, fosinopril, lisinopril, and quinapril. There were no significant differences between ramipril and perindopril *(Pilote et al 2004).*
  - In meta-regression analyses of 26 large-scale trials, ACE-Is and ARBs appeared to have similarly beneficial BP-dependent effects for risk reduction of stroke, CHD, and HF *(Blood Pressure Lowering Treatment Trialists' Collaboration 2007).*
  - For patients with mitral regurgitation secondary to MI, both ACE-Is and ARBs have been shown to improve prognosis *(Okura et al 2016).*
- Clinical trials have demonstrated the efficacy of ACE-Is in reducing mortality associated with congestive HF *(Cohn et al 1991, Dickstein et al 2002, Dobre et al 2008, Kober et al 1995, Lee et al 2004, McKelvie et al 1999, Packer et al 1999, Pfeffer et al 1992, Pfeffer et al 2003, Pitt et al 1997, Pitt et al 2000, The Acute Infarction Ramipril Efficacy [AIRE] Study Investigators 1993, The CONSENSUS Trial Study Group 1987, The SOLVD Investigators 1991, The SOLVD Investigators 1992, Tu et al 2005).*
  - No significant differences were noted when ACE-Is and ARBs were compared *(Dickstein et al 2002, Lee et al 2004, McKelvie et al 1999, Pfeffer et al 2003, Pitt et al 1997, Pitt et al 2000).*
- ACE-Is have also shown efficacy for protection against the development of progressive nephropathy in patients with DM *(Barnett et al 2004, Casas et al 2005, Hou et al 2007, Morgensen et al 2000, Ruggenenti et al 2004, The GISEN Group 1997, Wright et al 2002).*
  - In patients with type 2 DM, combination treatment with perindopril and indapamide reduced SBP and significantly decreased micro- and macrovascular events vs placebo *(ADVANCE Collaborative Group 2007, Zoungas et al 2014).*
  - In a meta-analysis comparing ACE-Is to ARBs for preventing the progression of diabetic kidney disease, the effects on renal outcomes were similarly beneficial between the groups *(Strippoli et al 2006).* In a meta-analysis of patients with CKD, including those with diabetic and nondiabetic nephropathy, both ACE-Is and ARBs reduced the risk of kidney failure compared to other active agents and placebo, and reduced CV events compared to placebo *(Xie et al 2016).* However, only ACE-Is reduced the risk of all-cause mortality compared to other active agents.
  - A meta-analysis of randomized antihypertensive trials in patients with DM and microalbuminuria found that reduction in albuminuria among normotensive patients was greatest with trandolapril plus candesartan, followed by trandolapril monotherapy. In hypertensive patients, reduction in albuminuria was greatest with fosinopril plus amlodipine, followed by fosinopril monotherapy. However, the combination therapies had inferior safety profiles when compared to ACE-I monotherapy with respect to dry cough, presyncope, and peripheral edema *(Huang et al 2017).*
  - In a recent trial enrolling adolescents with type 1 DM, the addition of an ACE-I did not change the albumin-to-creatinine ratio over 2 to 4 years of treatment vs placebo. However, the use of an ACE-I was associated with a lower incidence of microalbuminuria. The short duration of the trial was cited as an important limitation, and follow-up to evaluate the potential benefits of early intervention in this population is necessary *(Marcovecchio et al 2017).*
- Clinical trials have demonstrated the effectiveness of some ACE-I combination products compared to other ACE-I combination products or when compared to monotherapy *(Chrysant et al 2004, Chrysant et al 2007, Fogari et al 1997, Hilleman et al 1999, Jamerson et al 2004, Kuschnir et al 1996, Messerli et al 2000, Neutel et al 2005).*
  - Benazepril/amlodipine has demonstrated superior CV outcomes compared to benazepril/HCTZ *(Bakris et al 2010, Jamerson et al 2008, Weber et al 2010)*. In addition, benazepril/amlodipine has demonstrated higher antihypertensive efficacy compared to captopril/HCTZ *(Malacco et al 2002)* and olmesartan/HCTZ *(Kereiakes et al 2007).*

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Benazepril/amlodipine also demonstrated noninferiority to valsartan/HCTZ in lowering of DBP over 16 weeks in patients with HTN and DM *(Lee et al 2012).*

- When lisinopril/HCTZ was compared to a combination ARB, candesartan/HCTZ, no significant difference in antihypertensive efficacy was identified; however, the proportion of patients reporting at least 1 adverse event was significantly greater in the lisinopril/HCTZ group *(McInnes et al 2000).*
- Trandolapril/verapamil has been associated with a significantly greater reduction of BP compared to either component as monotherapy *(Brunner et al 2007, Cifkova et al 2000, Karlberg et al 2000, Pepine et al 2003, Pepine et al 2006, Ruggenenti et al 2004).*
- In 728 black patients from sub-Saharan Africa, blood pressure reductions were greater with amlodipine/HCTZ and amplodipine/perindopril than perindopril/HCTZ at 6 months (*Ojji et al 2019*).

- Studies have demonstrated that the combination of 2 renin angiotensin-aldosterone system (RAAS) inhibitors, including an ACE-I combined with an ARB, provides no renal or CV benefits and may lead to significant adverse events, particularly in patients with diabetes and/or renal insufficiency. Most notably, patients receiving combination therapy had increased rates of hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use *(Fried et al 2013, ONTARGET Investigators 2008, Parving et al 2012, Pfeffer et al 2003, Sakata et al 2015).*

CLINICAL GUIDELINES

- The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults *(Whelton et al 2018)* offers updated classifications of HTN and goals of treatment (see Table 4).

Table 4. Classification of BP measurements

BP Category	BP	Treatment or follow-up
Normal	SBP < 120 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate yearly; promote optimal lifestyle habits.
Elevated	SBP 120 - 129 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate in 3 to 6 months; lifestyle changes are recommended.
HTN stage 1	SBP 130 - 139 mm Hg *or* DBP 80 - 89 mm Hg	▪ Assess the 10-year risk for heart disease and stroke using the ASCVD risk calculator. ▪ If ASCVD risk is < 10%, lifestyle changes are recommended. A BP target of < 130/80 mm Hg may be reasonable. ▪ If ASCVD risk is ≥ 10%, or the patient has known CVD, DM, or CKD, lifestyle changes and 1 BP-lowering medication are recommended. A target BP of < 130/80 mm Hg is recommended.
HTN stage 2	SBP ≥ 140 mm Hg *or* DBP ≥ 90 mm Hg	▪ Lifestyle changes and BP-lowering medication from 2 different classes are recommended.

Abbrv: ASCVD=atherosclerotic cardiovascular disease, BP=blood pressure, CKD=chronic kidney disease, CVD=cardiovascular disease, DBP=diastolic blood pressure, DM=diabetes mellitus, HTN=hypertension, SBP=systolic blood pressure

- In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
  - First-line antihypertensive agents include: thiazide diuretics, CCBs, and ACE-Is or ARBs.
  - Diuretics, ACE-Is, ARBs, CCBs, and β-blockers have been shown to prevent CVD compared with placebo.
    - ACE-Is were notably less effective in preventing HF and stroke compared with CCBs in black patients. ARBs may be better tolerated than ACE-Is in black patients, with less cough and angioedema, but they offer no proven advantage over ACE-Is in preventing stroke or CVD in this population; thiazide diuretics (especially chlorthalidone) or CCBs are the best initial choice for single-drug therapy in this population, or as initial agents in a multidrug regimen.
  - An ACE-I is a preferred drug for treatment of HTN for those with CKD stage 3, or for stage 1 or 2 with albuminuria.

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- The American Diabetes Association position statement on DM and HTN recommends that most patients with DM and HTN be treated to a goal BP of < 140/90 mm Hg. Lower BP targets such as < 130/80 mm Hg may be appropriate for individuals at high risk of CVD *(American Diabetes Association 2019, de Boer et al 2017)*.
  - Treatment for HTN should include drug classes demonstrated to reduce CV events in patients with DM: ACE-Is, ARBs, thiazide diuretics, or dihydropyridine CCBs.
  - Patients with BP ≥ 160/100 mm Hg should have prompt initiation of 2 drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with DM.
  - An ACE-I or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for HTN in patients with DM and a urine albumin-to-creatinine ratio ≥ 30 mg/g creatinine.
- The American Academy of Pediatrics clinical practice guideline for high BP in children and adolescents recommends that the treatment goal with nonpharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to < 90th percentile and < 130/80 mm Hg in adolescents ≥ 13 years old *(Flynn et al 2017)*.
  - In hypertensive children and adolescents who have failed lifestyle modifications, clinicians should initiate pharmacologic treatment with an ACE-I, ARB, long-acting CCB, or thiazide diuretic.
  - Children and adolescents with CKD, HTN, and proteinuria should be treated with an ACE-I or ARB.
- Various other guidelines and position statements place ACE-Is as first-line therapy in patients with DM and microalbuminuria; with stable CAD and HTN; with HF; and after an MI. ACE-Is have demonstrated clinical benefit and reductions in morbidity and mortality in these populations *(Amsterdam et al 2014, Go et al 2014, Rosendorff et al 2015, Weber et al 2014, Yancy et al 2017).*
  - Due to differences in the activity of the RAAS, ACE-Is are often less effective as HTN monotherapy in black patients (African or Caribbean descent). Alternative first-line options for these patients include CCBs and thiazide diuretics *(Weber et al 2014).*

SAFETY SUMMARY

Boxed Warnings

- When pregnancy is detected, ACE-Is should be discontinued as soon as possible. Drugs that act directly on the RAAS can cause injury and death to the developing fetus.

Contraindications

- ACE-Is are contraindicated in patients with angioedema or with a history of hereditary or idiopathic angioedema.
- ACE-Is are contraindicated in combination with a neprilysin inhibitor (eg, sacubitril). An ACE-I should not be administered within 36 hours of a neprilysin inhibitor.
- ACE-Is are contraindicated in combination with aliskiren in patients with DM; the combination should also be avoided in patients with renal impairment (glomerular filtration rate [GFR] < 60 mL/min/1.73m^2).
- ACE-I combinations with HCTZ are contraindicated in patients with anuria.
- Due to the verapamil component, trandolapril/verapamil is contraindicated in patients with severe LV dysfunction, hypotension or cardiogenic shock, sick sinus syndrome, second or third degree atrioventricular (AV) block, patients with atrial flutter or fibrillation and an accessory bypass, and patients taking flibanserin.

Warnings and Precautions

- ACE-Is have warnings for anaphylactoid reactions including head and neck angioedema and intestinal angioedema; hypotension; hyperkalemia; and cholestatic jaundice and hepatic failure.
  - Captopril has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated HTN, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials are insufficient to show that other ACE-Is do not cause agranulocytosis at similar rates.
- Verapamil has a negative inotropic effect, which is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. However, congestive HF and/or pulmonary edema have been reported. Verapamil-containing products should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%, pulmonary wedge pressure > 20 mm Hg, or severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a β-blocker.
- Perindopril/amlodipine is not recommended in patients with HF. Use caution with amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

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- HCTZ may alter glucose tolerance and raise levels of cholesterol, triglycerides, and serum uric acid levels (which may precipitate gout). HCTZ may cause elevations of serum calcium and monitoring is recommended in patients with hypercalcemia.

Adverse Effects
- Common adverse effects of ACE-Is include headache, dizziness, cough, and hypotension.
- ACE-Is may cause electrolyte abnormalities and elevations of blood urea nitrogen (BUN) and creatinine.
- Some combination products contain amlodipine, which may cause peripheral edema.

Important Drug Interactions
- Dual blockade of the RAAS with ARBs, ACE-I, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure), compared to monotherapy.
  - Most patients receiving the combination of 2 RAAS inhibitors do not obtain any additional benefit compared to monotherapy.
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of non-steroidal anti-inflammatory agents (NSAIDs) with ACE-Is may result in deterioration of renal function, including acute renal failure. The antihypertensive effect of ACE-Is may be attenuated by NSAIDs.
- Concomitant use of ACE-Is and potassium-sparing diuretics (eg, spironolactone, amiloride, triamterene) can increase the risk of hyperkalemia.
- Patients taking mammalian target of rapamycin (mTOR) inhibitors (eg, temsirolimus, sirolimus, everolimus) or a neprilysin inhibitor may be at increased risk for angioedema with concomitant ACE-I use.
- Verapamil has drug interactions with colchicine, digoxin, immunosuppressants, and several others. Consult the prescribing information for trandolapril/verapamil for the full listing and descriptions.

DOSING AND ADMINISTRATION

- All ACE-I-containing products, with the exception of fosinopril, require dosage adjustment in patients with renal impairment.
- The combination ACE-I products are not recommended for use in patients with severe renal impairment and should be used with caution in patients with hepatic impairment.
- Breastfeeding is not recommended while on ACE-I-containing products.

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity ACE-Is				
benazepril	Tablets	Oral	HTN: Once or twice daily	FDA-approved for use in children ≥ 6 years.
captopril	Tablets	Oral	Diabetic nephropathy, HF, LV dysfunction after MI: Three times daily HTN: Twice to 3 times daily	Take 1 hour before meals or 2 hours after meals.
enalapril	Tablets, 1 mg/mL oral solution	Oral	Asymptomatic LV dysfunction, HF: Twice daily HTN: Daily in 1 or 2 divided doses	FDA-approved for use in children aged ≥ 1 month.
enalaprilat	Injection	IV	HTN: Every 6 hours	Administer as a slow IV infusion or as an IV bolus over 5 minutes.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
fosinopril	Tablets	Oral	HF: Once daily HTN: Daily in 1 or 2 divided doses	FDA-approved for use in children ≥ 6 years weighing more than 50 kg.
lisinopril	Tablets, 1 mg/mL solution	Oral	AMI to improve survival, HF, HTN: Once daily	FDA-approved for use in children ≥ 6 years.
moexipril	Tablets	Oral	HTN: Daily in 1 or 2 divided doses	Take 1 hour before meals.
perindopril	Tablets	Oral	HTN: Daily in 1 or 2 divided doses Stable CAD: Once daily	Bioavailability of perindopril is higher with hepatic impairment. Dosage adjustment in elderly patients is required.
quinapril	Tablets	Oral	HF: Twice daily HTN: Daily in 1 or 2 divided doses	Dosage adjustment in elderly patients is required.
ramipril	Capsules	Oral	HF after MI: Twice daily HTN: Daily in 1 or 2 divided doses Reduce risk of MI, stroke, and death from CV causes: Once daily	Capsules should be swallowed whole; capsule contents can be sprinkled on applesauce or mixed in 120 mL of water or apple juice.
trandolapril	Tablets	Oral	HF or LV dysfunction after MI: Once daily HTN: Once to twice daily	Dosage adjustment in hepatic impairment is required.
ACE-I/HCTZ Combinations*				
benazepril/HCTZ	Tablets	Oral	HTN: Once daily	
captopril/HCTZ	Tablets	Oral	HTN: Once daily	Take 1 hour before a meal or 2 hours after meals.
enalapril/HCTZ	Tablets	Oral	HTN: Once daily	
fosinopril/HCTZ	Tablets	Oral	HTN: Once daily	
lisinopril/HCTZ	Tablets	Oral	HTN: Once daily	
moexipril/HCTZ	Tablets	Oral	HTN: Once daily	Take 1 hour before a meal.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
quinapril/HCTZ	Tablets	Oral	HTN: Once daily	
ACE-I/CCB Combinations*				
benazepril/amlodipine	Capsules	Oral	HTN: Once daily	Exposure is increased in elderly patients and in hepatic dysfunction; a lower dosage should be considered.
perindopril/amlodipine	Tablets	Oral	HTN: Once daily	Exposure is increased in elderly patients and in hepatic dysfunction; a lower maximum dosage should be considered in elderly patients.
trandolapril/verapamil	Tablets, extended-release	Oral	HTN: Once daily	Administer with food.

Abbrv: ACE-I=angiotensin converting enzyme inhibitor, AMI=acute myocardial infarction, CAD=coronary artery disease, CCB=calcium channel blocker, CV=cardiovascular, FDA=Food and Drug Administration, HCTZ=hydrochlorothiazide, HF=heart failure, HTN=hypertension, IV=intravenous, LV=left ventricular, MI=myocardial infarction

*Captopril/HCTZ and perindopril/amlodipine are the only combination ACE-Is that are FDA-approved for use as initial HTN therapy. 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.

See the current prescribing information for full details.

CONCLUSION

- The single-entity and combination ACE-I products are FDA-approved for the treatment of HTN, and most are generically available. Most single-entity ACE-Is are also approved for the treatment of HF. With the exception of captopril/HCTZ and perindopril/amlodipine, the combination ACE-Is are not approved for use as initial HTN therapy.
- Evidence-based guidelines recognize the important role ACE-Is play in the treatment of HTN and other CV and renal diseases. There is no consensus on BP goals for certain populations such as older patients and patients with DM. The current ACC/AHA guidelines *(Whelton et al 2018)* recommend a BP goal of < 130/80 mm Hg for most patients.
- ACE-Is have demonstrated efficacy in the treatment of HTN, for protection against progressive nephropathy in patients with DM, for reducing mortality associated with HF, and for reducing the risk of CV mortality, MI, and stroke in patients with CAD.
  - ACE-Is have generally demonstrated comparable efficacy to ARBs across indications.
- Studies have demonstrated that the combination of 2 RAAS inhibitors, including an ACE-I with an ARB, provides no renal or CV benefits and may increase risk of adverse events, including hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use.
- All ACE-Is have a boxed warning for use in pregnancy and are contraindicated in patients with a history of angioedema. Other warnings include anaphylactoid reactions including head and neck angioedema, hypotension, hyperkalemia, and cholestatic jaundice and hepatic failure.
- Common adverse effects of ACE-Is include headache, dizziness, cough, and hypotension. ACE-Is may cause electrolyte abnormalities and increases in BUN and creatinine.
- Current guidelines recommend ACE-Is as a first-line therapy for patients with HTN, DM with microalbuminuria, stable CAD with HTN, HF, and post-MI *(American Diabetes Association 2019, Amsterdam et al 2014, de Boer et al 2017, Go et al 2014, Rosendorff et al 2015, Weber et al 2014, Whelton et al 2018, Yancy et al 2017).*
  - Due to differences in the activity of the RAAS, ACE-Is are often less effective as HTN monotherapy in black patients; CCBs and thiazide diuretics should be used as first-line options in these patients.

REFERENCES

- Accupril [package insert], New York, NY: Pfizer, Inc.; July 2017.
- Accuretic [package insert], New York, NY: Pfizer, Inc.; July 2017.

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- ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet.* 2007;370:829–840.
- Altace [package insert], New York, NY: Pfizer, Inc.; February 2018.
- American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes: 2019. *Diabetes Care*. 2019;42(Suppl 1):S103-S123. doi: 10.2337/dc19-S010.
- Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;130e:e344-426.
- Bakris GL, Sarafidis PA, Weir MR, et al.; ACCOMPLISH Trial investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomized controlled trial. *Lancet.* 2010 Apr 3;375(9721):1173-81.
- Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med*. 2004;351:1953-61.
- Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-5528. doi: 10.1161/CIR.0000000000000659.
- Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. *J Hypertens*. 2007 Jun;25(5):951-8.
- Brunner M, Cooper-DeHoff RM, Gong Y, et al; for the INVEST Investigators. Factors influencing blood pressure response to trandolapril add-on therapy in patients taking verapamil SR (from the International Verapamil SR/Trandolapril [INVEST] Study). *Am J Cardiol*. 2007;99:1549-54.
- Captopril [package insert], Melville, NY; Amici Pharmaceuticals LLC; June 2019.
- Captopril HCTZ [package insert], Morgantown, WV: Mylan Pharmaceuticals Inc., March 2006.
- Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet.* 2005;366:2026-33.
- Chrysant SG, Bakris GL. Amlodipine/benazepril combination therapy for hypertensive patients nonresponsive to benazepril monotherapy. *Am J Hypertens*. 2004 Jul;17(7):590-6.
- Chrysant SG, Sugimoto DH, Lefkowitz M, et al. The effects of high-dose amlodipine/benazepril combination therapies on blood pressure reduction in patients not adequately controlled with amlodipine monotherapy. *Blood Press Suppl*. 2007 Mar;1:10-7.
- Cifkova R, Nakov R, Novozamska E, et al. Evaluation of the effects of fixed combinations of sustained-release verapamil/trandolapril versus Kober/hydrochlorothiazide on metabolic and electrolyte parameters in patients with essential hypertension. *J Hum Hypertens*. 2000;14:347-54.
- Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med.* 1991;325:303-10.
- Dahlof B, Sever PS, Poulter NR, et al; for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet*. 2005;366(9489):895-906.
- de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care.* 2017;40:1273-84.
- Dickstein K, Kjekshus J; for the OPTIMAAL Steering Committee, for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. *Lancet.* 2002;360:752-60.
- Dobre D, van Veldhuisen DJ, Goulder MA, et al. Clinical effects of initial 6 months monotherapy with bisoprolol versus enalapril in the treatment of patients with mild to moderate chronic heart failure. Data from the CIBIS III Trial. *Cardiovasc Drugs Ther*. 2008;22(5):399-405.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 15, 2019.
- Enalaprilat [package insert], Lake Forest, IL: Hospira, Inc.; June 2018.
- Epaned [package insert], Greenwood Village, CO: Silvergate Pharmaceuticals, Inc.; December 2018.
- Flynn JT, Kaelber DB, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904
- Fogari R, Corea L, Cardoni O, et al. Combined therapy with benazepril and amlodipine in the treatment of hypertension inadequately controlled by an ACE inhibitor alone. *J Cardiovasc Pharmacol*. 1997 Oct;30(4):497-503.
- Fosinopril [package insert], Sunrise, FL; Cipla USA, Inc.; May 2017.
- Fosinopril HCTZ [package insert], East Windsor, NJ; Aurobindo Pharma USA, Inc.; September 2018.
- Fox KM, Bertrand M, Ferrari R, et al; for the EUROPA Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-8.
- Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy (VA NEPHRON-D). *N Engl J Med*. 2013;369:1892-903.
- Go AS, Bauman M, King SM, et al. An Effective Approach to High Blood Pressure Control: A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA/ACC/CDC). *Hypertension*. 2014;63(4)878-85.
- Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. *Cochrane Database Syst Rev*. 2008;(4):CD003823.
- Hilleman DE, Ryschon KL, Mohiuddin SM, Wurdeman RL. Fixed-dose combination vs monotherapy in hypertension: a meta-analysis evaluation. *J Hum Hypertens*. 1999;13(7):477-83.
- Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal antiproteinuric doses (ROAD) study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol*. 2007;18:1889-98.
- Huang R, Feng Y, Wang Y, et al. Comparative efficacy and safety of antihypertensive agents for adult diabetic patients with microalbuminuric kidney disease: a network meta-analysis. *PLoS One*. 2017;3:12(1):e0168582. doi: 10.1371/journal.pone.0168582.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Jamerson K, Weber MA, Bakris GL, et al; for the ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359(23):2417-28.
- Jamerson KA, Nwose O, Jean-Louis L, et al. Initial angiotensin-converting enzyme inhibitor/calcium channel blocker combination therapy achieves superior blood pressure control compared with calcium channel blocker monotherapy in patients with stage 2 hypertension. *Am J Hypertens*. 2004;17(6):495-501.
- Karlberg BE, Andrup M, Oden A; for the Swedish Tarka Trialists. Efficacy and safety of a new long-acting drug combination, trandolapril/verapamil as compared to monotherapy in primary hypertension. *Blood Pressure*. 2000;9:140-5.
- Kereiakes DJ, Neutel JM, Punzi HA, et al. Efficacy and safety of olmesartan medoxomil and hydrochlorothiazide compared with benazepril and amlodipine besylate. *Am J Cardiovasc Drugs*. 2007;7(5):36-72.
- Kober L, Torp-Pedersen C, Carlsen JE, et al; for the Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 1995;333(25):1670-6.
- Kuschnir E, Acuna E, Sevilla D, et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 20 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo. *Clin Ther*. 1996;18(6):1213-24.
- Lee IT, Hung YJ, Chen JF, et al. Comparison of the efficacy and safety profiles of two fixed-dose combinations of antihypertensive agents, amlodipine/benazepril versus valsartan/hydrochlorothiazide, in patients with type 2 diabetes mellitus and hypertension: a 16-week, multicenter, randomized, double-blind, noninferiority study. *Clin Ther.* 2012;34(8):1735-50.
- Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med*. 2004;141(9):693-704.
- Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev*. 2014 Aug 22;(8):CD009096. doi: 10.1002/14651858.CD009096.pub2.
- Lotensin [package insert], Parsippany, NJ; Validus Pharmaceuticals LLC; January 2019.
- Lotensin HCT [package insert], Parsippany, NJ; Validus Pharmaceuticals LLC; August 2018.
- Lotrel [package insert], East Hanover, NJ: Novartis; July 2017.
- Malacco E, Piazza S, Carretta R, et al; for the Italian Blood Pressure Study Group. Comparison of benazepril-amlodipine and captopril-thiazide combinations in the management of mild-to-moderate hypertension. *Int J Clin Pharmacol Ther*. 2002;40(6):263-9.
- Marcovecchio ML, Chiesa ST, Bond S, et al. ACE inhibitors and statins in adolescents with type 1 diabetes. *New Engl J Med.* 2017;377:1733-45.
- McInnes GT, O'Kane KP, Istad H, et al. Comparison of the AT1-receptor blocker, candesartan cilexetil, and the ACE inhibitor, lisinopril, in fixed combination with low dose hydrochlorothiazide in hypertensive patients. *J Hum Hypertens*. 2000;14(4):263-9.
- McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study: the RESOLVD Pilot Study Investigators. *Circulation.*1999;100:1056-64.
- Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) versus high-dose calcium antagonist monotherapy for systemic hypertension. *Am J Cardiol.* 2000;86:1182-7.
- Moexipril [package insert], North Wales, PA: Teva; August 2015.
- Moexipril HCTZ [package insert], Eatontown, NJ: Heritage Pharmaceuticals Inc.; October 2017.
- Morgensen CE, Neldam S, Tikkansen I, et al. Randomized controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ*. 2000;321:1440-4.
- Neutel JM, Smith DH, Weber MA, et al. Efficacy of combination therapy for systolic blood pressure in patients with severe systolic hypertension: Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT) study. *J Clin Hypertens*. 2005;7(11):641-6.
- Nissen SE, Tuzcu EM, Libby P, et al; for the CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292(18):2217-26.
- Ojji DB, Mayosi B, Francis V, et al for the CREOLE Study Investigators. Comparison of dual therapies for lowering blood pressure in black Africans. *N Engl J Med*. 2019;380(25):2429-2439.
- Okura H, Kataoka T, Yoshida K. Renin-angiotensin system inhibitors in patients with myocardial infarction and secondary mitral regurgitation. *Heart.* 2016;102:649-700.
- ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-59.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed November 15, 2019.
- Packer M, Poole-Wilson PA, Armstrong PW, et al; on behalf of the ATLAS Study Group. Comparative effects of low and high doses of angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation*. 1999;100:2312-18.
- Parving H, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes (ALTITUDE). *N Engl J Med.* 2012;367(32):2204.
- Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease: the international verapamil-trandolapril study (INVEST): a randomized controlled trial. *JAMA*. 2003;290(21):2805-16.
- Pepine CJ, Kowey PR, Kupfer S, et al. Predictors of adverse outcome among patients with hypertension and coronary artery disease. *J Am Coll Cardiol*. 2006;47(3):547-51.
- Perindopril [package insert], Eatontown, NJ: West-Ward Pharmaceuticals Corp.; March 2019.
- Pfeffer MA, Braunwald E, Moye LA, et al; on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med*. 1992;327(10):669-77.
- Pfeffer MA, McMurray JJV, Velazquez EJ, et al; for the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-906.
- Pilote L, Abrahamowicz M, Rodrigues E, et al. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? *Ann Intern Med*. 2004;141(2):102-12.
- Pitt B, Poole-Wilson PA, Segal R, et al; on behalf of the ELITE II Investigators. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial–the Losartan Heart Failure Survival Study, ELITE II. *Lancet*. 2000;355:1582–7.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Pitt B, Reichek N, Willenbrock R, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation*. 2003;108(15):1831-8.
- Pitt B, Segal R, Martinez FA, et al; for the ELITE Study Investigators. Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet.* 1997;349:747–52.
- PREAMI Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized perindopril and remodeling in elderly with acute myocardial infarction (PREAMI) study. *Arch Intern Med.* 2006;166:659-66.
- Prestalia [package insert], Durham, NC: Adhera Therapeutics, Inc.; August 2019.
- Prinivil [package insert], Whitehouse Station, NJ: Merck & Co., Inc.; November 2019.
- PROGRESS Collaborative group. Randomized trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. *Lancet*. 2001;358:1033-41.
- Qaseem A, Witt TJ, Rich R, et al. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med.* 2017;166(6):430-437.
- Qbrelis [package insert], Greenwood Village, CO: Silvergate Pharmaceuticals, Inc.; December 2018.
- Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension (AHA/ACC/ASH). *J Am Coll Cardiol.* 2015;65(18):1998-2038.
- Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med.* 2004;351(19):1941-51.
- Sakata Y, Shiba N, Takahashi J, et al. Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial. *Eur Heart J.* 2015;36(15):915-23.
- Sanders GD, Coeytaux R, Dolor RJ, et al. Angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor antagonists (ARBs), and direct renin inhibitors for treating essential hypertension: an update. Comparative Effectiveness Review No. 34. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025.) AHRQ Publication No. 11-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011.
- Savarese G, Costanzo P, Cleland JG, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol*. 2013;61(2):131-42.
- SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015; 373(22):2103-16.
- Strippoli GFM, Bonifati C, Craig M, et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease (review). *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD006257.
- Swedberg K, Held P, Kjekshus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction results of the cooperative New Scandinavian enalapril survival study II (CONSENSUS II). *N Engl J Med*. 1992;327(10):678-84.
- Tarka [package insert], North Chicago, IL: AbbVie Inc.; September 2019.
- The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet*. 1993;342:821-8.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the cooperative North Scandinavian enalapril survival study. *N Engl J Med*. 1987;316(23):1429-35.
- The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomized placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet.* 1997;349:1857–63.
- The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145-53.
- The PEACE Trial Investigators. Angiotensin-converting enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351(20):2058-68.
- The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327(10):685-91.
- The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293-302.
- Trandolapril [package insert]. Saddle Brook, NJ: Rising Health, LLC; January 2018.
- Tu K, Mamdani M, Kopp A, et al. Comparison of angiotensin-converting enzyme inhibitors in the treatment of congestive heart failure. *Am J Cardiology.* 2005;95:283-6.
- van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. *Eur Heart J.* 2012;33(16):2088-97.
- Vaseretic [package insert], Bridgewater, NJ: Valeant Pharmaceuticals LLC; July 2017.
- Vasotec [package insert], Bridgewater, NJ: Valeant Pharmaceuticals LLC; November 2018.
- Weber MA, Bakris GL, Jamerson K, et al; for the ACCOMPLISH Investigators. Cardiovascular events during differing hypertension therapies in patients with diabetes. *J Am Coll Cardiol*. 2010;56(1):77-85.
- Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH). *J Hypertens*. 2014;32(1):3-15.
- Wells T, Frame V, Soffer B, et al. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. *J Clin Pharmacol*. 2002;42(8):870-80.
- Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71(6):e13-e115.
- Wright JT Jr, Bakris G, Greene T, et al. Effects of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288(19):2421-31.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Xie A, Liu Y, Perkovic V, et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a Bayesian network meta-analysis of randomized clinical trials. *Am J Kidney Dis.* 2016;67(5):728-741.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. 2017;23(8):628-651. doi: 10.1016/j.jacc.2017.04.025.
- Zestoretic [package insert], Pine Brook, NJ: Almatica Pharma, Inc.; July 2017.
- Zestril [package insert], Pine Brook, NJ: Almatica Pharma, Inc.; October 2018.
- Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med*. 2014; 371(15):1392-406.

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