

## Therapeutic Class Overview

### Angiotensin-Converting Enzyme (ACE) Inhibitors

#### INTRODUCTION

- Approximately 126.9 million American adults are living with some form of cardiovascular (CV) disease (coronary heart disease, heart failure [HF], stroke, and hypertension), according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2021 update (Virani et al 2021). Cardiovascular 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 (Virani et al 2021). The 2017 American College of Cardiology (ACC)/AHA Clinical Practice Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults defines HTN as a blood pressure (BP)  $\geq$  130/80 mm Hg (Whelton et al 2018). Nearly half of American adults 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 (Eckel et al 2013, Virani et al 2021).
- 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 ( $\beta$ )-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 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, Whelton et al 2018, Unger et al 2020).
- In general, guideline-recommended BP goals in hypertensive adults range from  $<$  130/80 mm Hg to  $<$  140/90 mm Hg (American Diabetes Association [ADA] 2021, Arnett et al 2019, de Boer et al 2017, Unger et al 2020, Whelton et al 2018).
  - Blood pressure goals for older patients have long been a point of debate. The SPRINT trial followed patients  $\geq$  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  $\geq$  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

**Table 1. Medications Included Within Class Review**

Drug	Generic Availability
<b>Single-Entity ACE-Inhibitors</b>	
Accupril (quinapril)	✓
Altace (ramipril)	✓
captopril*	✓
enalaprilat*	✓
fosinopril*	✓
Lotensin (benazepril)	✓
moexipril*	✓
perindopril*	✓
Prinivil, Qbrelis, Zestril (lisinopril)	✓ (Prinivil and Zestril only)
trandolapril*	✓
Vasotec, Epaned (enalapril)‡	✓
<b>ACE-I/HCTZ Combinations</b>	
Accuretic (quinapril/HCTZ)	✓
captopril/HCTZ*	✓
fosinopril/HCTZ*	✓
Lotensin HCT (benazepril/HCTZ)	✓
Vaseretic (enalapril/HCTZ)	✓
Zestoretic (lisinopril/HCTZ)†	✓
<b>ACE-I/CCB Combinations</b>	
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), and Monopril HCT (fosinopril/HCTZ) are no longer marketed.

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

‡As of August 2021, a generic for Epaned (enalapril) oral solution launched. All enalapril formulations are available as brand or generics.

([Drugs@FDA 2021](#), [Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021](#))

## 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		✓										✓
Stable coronary artery disease to reduce the risk of CV mortality or nonfatal MI								✓				

Data as of May 15, 2021 MG-U/PH-U/RLP/LMR

Page 2 of 13

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Indication	benazepril	captopril	enalapril/ enalaprilat	Epaned (enalapril)	fosinopril	lisinopril	moexipril	perindopril	Qbrelis (lisinopril)	quinapril	ramipril	trandolapril
Reduce risk of MI, stroke, and death from CV causes in patients ≥ 55 years of age at high risk for a major CV event											✓	

Abbrev: 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<sup>2</sup>.

†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 2019, Altace 2017, captopril 2020, enalaprilat 2021, Epaned 2020, fosinopril 2021, Lotensin 2019, moexipril 2015, perindopril 2019, Prinivil 2019, Qbrelis 2020, trandolapril 2018, Vasotec 2020, Zestril 2020)

**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
<b>ACE-I/HCTZ Combinations</b>				
benazepril/HCTZ	✓			
captopril/HCTZ			✓	
enalapril/HCTZ	✓			
fosinopril/HCTZ	✓			
lisinopril/HCTZ	✓			
quinapril/HCTZ	✓			
<b>ACE-I/CCB Combinations</b>				
benazepril/amlodipine		✓		
perindopril/amlodipine*				✓
trandolapril/verapamil ER	✓			

Abbrev: 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 2021, captopril/HCTZ 2020, fosinopril/HCTZ 2020, Lotensin HCT 2020, Lotrel 2021, Prestalia 2019, Tarka 2019, Vasoretic 2020, Zestoretic 2020)

- 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 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*). 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 amlodipine/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*).
- One meta-analysis compared the effectiveness of ACE-Is with ARBs and found that the 2 drug classes had similar effectiveness in lowering SPB and DBP, all-cause mortality, essential hypertension, fatal and non-fatal MI, and stroke. ACE-Is were more helpful in the prevention of and/or during hospitalization for heart failure than ARBs (*Dimou et al 2019*).

#### 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 (Table 4).

**Table 4. Classification of BP measurements**

BP Category	BP	Treatment or follow-up
<b>Normal</b>	SBP < 120 mm Hg and DBP < 80 mm Hg	<ul style="list-style-type: none"> <li>▪ Evaluate yearly; promote optimal lifestyle habits.</li> </ul>
<b>Elevated</b>	SBP 120 - 129 mm Hg and DBP < 80 mm Hg	<ul style="list-style-type: none"> <li>▪ Evaluate in 3 to 6 months; lifestyle changes are recommended.</li> </ul>
<b>HTN stage 1</b>	SBP 130 - 139 mm Hg or DBP 80 - 89 mm Hg	<ul style="list-style-type: none"> <li>▪ Assess the 10-year risk for heart disease and stroke using the ASCVD risk calculator.</li> <li>▪ If ASCVD risk is &lt; 10%, lifestyle changes are recommended. A BP target of &lt; 130/80 mm Hg may be reasonable.</li> <li>▪ 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 &lt; 130/80 mm Hg is recommended.</li> </ul>
<b>HTN stage 2</b>	SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg	<ul style="list-style-type: none"> <li>▪ Lifestyle changes and BP-lowering medication from 2 different classes are recommended.</li> </ul>

Abbrev: 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.
- The 2019 ACC/AHA guideline on the primary prevention of CVD recommends using BP-lowering medications in hypertensive adults: with an estimated 10-year ASCVD risk  $\geq 10\%$  and a SBP  $\geq 130$  mm Hg or DBP  $\geq 80$  mm Hg; with diabetes and a BP  $> 130/80$  mm Hg; or with an estimated 10-year ASCVD risk  $< 10\%$  and a SBP  $\geq 140$  mm Hg or DBP  $\geq 90$  mm Hg (Arnett et al 2019). A target BP of  $< 130/80$  mm Hg is recommended for most patients.
- The ADA 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. Target BPs should be individualized and lower BP targets such as  $< 130/80$  mm Hg may be appropriate for individuals at high risk of CVD (ADA 2021, 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  $\geq 160/100$  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  $\geq 30$  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  $< 90^{\text{th}}$  percentile and  $< 130/80$  mm Hg in adolescents  $\geq 13$  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, Arnold et al 2020, Go et al 2014, Rosendorff et al 2015, Unger et al 2020, 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 (or a CCB with an ARB) (Unger et al 2020).

## 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<sup>2</sup>).
- 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  $\beta$ -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.
- 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.
  - HCTZ is associated with an increased risk of non-melanoma skin cancer.

#### 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 **drugs** (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
<b>Single-Entity ACE-Is</b>				
benazepril	Tablets	Oral	HTN: Once or twice daily	FDA-approved for use in children $\geq$ 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.
enalapril	Tablets, 1 mg/mL oral solution	Oral	Asymptomatic LV dysfunction, HF:	FDA-approved for use in children aged $\geq$ 1 month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Twice daily <u>HTN:</u> Daily in 1 or 2 divided doses	
enalaprilat	Injection	IV	<u>HTN:</u> Every 6 hours	Administer as a slow IV infusion or as an IV bolus over 5 minutes.
fosinopril	Tablets	Oral	<u>HF:</u> Once daily <u>HTN:</u> Daily in 1 or 2 divided doses	FDA-approved for use in children $\geq$ 6 years weighing more than 50 kg.
lisinopril	Tablets, 1 mg/mL solution	Oral	<u>AMI to improve survival, HF,</u> <u>HTN:</u> Once daily	FDA-approved for use in children $\geq$ 6 years.
moexipril	Tablets	Oral	<u>HTN:</u> Daily in 1 or 2 divided doses	Take 1 hour before meals.
perindopril	Tablets	Oral	<u>HTN:</u> Daily in 1 or 2 divided doses <u>Stable CAD:</u> Once daily	Bioavailability of perindopril is higher with hepatic impairment.  Dosage adjustment in elderly patients is required.
quinapril	Tablets	Oral	<u>HF:</u> Twice daily <u>HTN:</u> Daily in 1 or 2 divided doses	Dosage adjustment in elderly patients is required.
ramipril	Capsules	Oral	<u>HF after MI:</u> Twice daily <u>HTN:</u> Daily in 1 or 2 divided doses <u>Reduce risk of MI, stroke, and death from CV causes:</u> 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	<u>HF or LV dysfunction after MI:</u> Once daily <u>HTN:</u> Once to twice daily	Dosage adjustment <b>with hepatic cirrhosis</b> is required.
<b>ACE-I/HCTZ Combinations*</b>				
benazepril/HCTZ	Tablets	Oral	<u>HTN:</u> Once daily	
captopril/HCTZ	Tablets	Oral	<u>HTN:</u> Once daily	Take 1 hour before a meal.
enalapril/HCTZ	Tablets	Oral	<u>HTN:</u> Once daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
fosinopril/HCTZ	Tablets	Oral	HTN: Once daily	
lisinopril/HCTZ	Tablets	Oral	HTN: Once daily	
quinapril/HCTZ	Tablets	Oral	HTN: Once daily	
<b>ACE-I/CCB Combinations*</b>				
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.

Abbrev: 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-I's 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-I's are also approved for the treatment of HF. With the exception of captopril/HCTZ and perindopril/amlodipine, the combination ACE-I's are not approved for use as initial HTN therapy.
- Evidence-based guidelines recognize the important role ACE-I's 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-I's 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-I's 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, provide 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-I's 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-I's include headache, dizziness, cough, and hypotension. ACE-I's may cause electrolyte abnormalities and increases in BUN and creatinine.
- Current guidelines recommend ACE-I's as a first-line therapy for patients with HTN, DM with microalbuminuria, stable CAD with HTN, HF, and post-MI (*ADA 2021, Amsterdam et al 2014, Arnett et al 2019, Arnold et al 2020, de Boer et al 2017, Go et al 2014, Rosendorff et al 2015, Unger et al 2020, Whelton et al 2018, Yancy et al 2017*).
  - Due to differences in the activity of the RAAS, ACE-I's are often less effective as HTN monotherapy in black patients; CCBs and thiazide diuretics should be used as first-line options in these patients.

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