



Department of Vermont Health Access

Therapeutic Class Review Angiotensin-Converting Enzyme (ACE) Inhibitors Combination Products

Overview/Summary

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/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 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 vasodilation 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 ACE inhibitors included in this review. This review encompasses all dosage forms and strengths. The brand name products Capozide[®] (captopril/hydrochlorothiazide) and Monopril HCT[®] (fosinopril/hydrochlorothiazide) have been discontinued; however, the generic products are still available. In 2008, the combination enalapril/felodipine (Lexxel[®]) was discontinued. All combination ACE inhibitors included in this review are available generically.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Benazepril/amlodipine (Lotrel ^{®*})	Combination angiotensin-converting enzyme inhibitors	✓
Benazepril/hydrochlorothiazide (Lotensin HCT ^{®*})	Combination angiotensin-converting enzyme inhibitors	✓

Generic Name (Trade Name)	Medication Class	Generic Availability
Captopril/hydrochlorothiazide*	Combination angiotensin-converting enzyme inhibitors	✓
Enalapril/hydrochlorothiazide (Vaseretic ^{®*})	Combination angiotensin-converting enzyme inhibitors	✓
Fosinopril/hydrochlorothiazide*	Combination angiotensin-converting enzyme inhibitors	✓
Lisinopril/hydrochlorothiazide (Prinzide ^{®*} , Zestoretic ^{®*})	Combination angiotensin-converting enzyme inhibitors	✓
Moexipril/hydrochlorothiazide (Uniretic ^{®*})	Combination angiotensin-converting enzyme inhibitors	✓
Quinapril/hydrochlorothiazide (Accuretic ^{®*})	Combination angiotensin-converting enzyme inhibitors	✓
Trandolapril/verapamil (Tarka ^{®*})	Combination angiotensin-converting enzyme inhibitors	✓

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

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications⁴⁻¹⁴

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
Benazepril/amlodipine		✓	
Benazepril/HCTZ	✓		
Captopril/HCTZ			✓
Enalapril/HCTZ	✓		
Fosinopril/HCTZ	✓		
Lisinopril/HCTZ	✓		
Moexipril/HCTZ	✓		
Quinapril/HCTZ	✓		
Trandolapril/verapamil	✓		

HCTZ=hydrochlorothiazide

Pharmacokinetics

The pharmacokinetic properties of the individual components of the combination angiotensin-converting enzyme inhibitors are outlined in table 3.

Table 3. Pharmacokinetics⁴⁻¹⁴

Generic Name	Bioavailability (%)	Protein Binding (%)	Elimination (%)	Active Metabolites	Half-Life (hours)
Angiotensin-Converting Enzyme Inhibitors					
Benazepril	≥37	~96*	Bile (11 to12)*; renal (20)*	Yes; benazeprilat	10 to11*
Captopril	≥75	~25 to 30	Renal (>95)	None	<2
Enalapril	~60	50 to 60	Feces; renal (60 to 80)	Yes, enalaprilat	11*
Fosinopril	~36	~ 100*	Feces (50); renal (50)	Yes, fosinoprilat	12*
Lisinopril	~25	None	Renal (100)	None	12
Moexipril	~13	~50*	Feces (53);	Yes,	2 to 9*

Generic Name	Bioavailability (%)	Protein Binding (%)	Elimination (%)	Active Metabolites	Half-Life (hours)
			renal (13)	moexiprilat	
Quinapril	≥60	~97	Renal	Yes, quinaprilat	2*
Trandolapril	10 (70)*	80	Feces (66); renal (33)	Yes, trandolaprilat	6 (10)*
Diuretics					
Hydro-chlorothiazide	~50 to 80	68	Renal (as unchanged drug)	No	6 to 15
Calcium-Channel Blocking Agents					
Amlodipine	64 to 90	93	Renal (10 parent, 60 inactive metabolites)	No	30 to 50
Verapamil	20 to 35	~90	Feces (≥16); renal (~70)	Yes, norverapamil	~12 (sustained release)

*Active metabolite.

Clinical Trials

Clinical trials have demonstrated the effectiveness of the angiotensin-converting enzyme inhibitor combination products compared to monotherapy.¹⁵⁻²² Benazepril/amlodipine has demonstrated “superior” cardiovascular outcomes compared to benazepril/hydrochlorothiazide.²³⁻²⁶ In addition, benazepril/amlodipine has shown a significant reduction in blood pressure compared to captopril/hydrochlorothiazide and olmesartan/hydrochlorothiazide.^{27,28} When lisinopril/hydrochlorothiazide was compared to a combination angiotensin receptor blocker, candesartan/hydrochlorothiazide, no significant difference in the change in blood pressure between the groups was found.²⁹ Trandolapril/verapamil has been associated with a significantly greater reduction of blood pressure compared to either component as monotherapy.³⁰⁻³⁵

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Messerli et al³⁶</p> <p>Benazepril/amlodipine 10/5 or 20/5 mg/day</p>	<p>OL, RCT</p> <p>Patients ≥18 years of age with mild-to-moderate hypertension currently taking amlodipine 5 or 10 mg with inadequate BP control (DBP ≥90 mm Hg, Group 1) or inability to tolerate amlodipine (DBP ≤90 mm Hg but with edema, Group 2)</p>	<p>N=7,912</p> <p>4 weeks</p>	<p>Primary: Group 1-change in mean sitting DBP</p> <p>Group 2- percentage of patients whose edema improved</p> <p>Secondary: Group 1-change in mean sitting SBP</p>	<p>Primary: In Group 1, mean reduction in DBP at week four was 11.5 mm Hg (95% CI, –11.8 to –11.3; <i>P</i><0.001). Mean DBP declined from 96.5 (baseline) to 84.9 mm Hg (at four weeks).</p> <p>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 <i>P</i> value reported).</p> <p>Secondary: In Group 1, mean reduction in SBP at week four was 15.6 mm Hg (95% CI, –16.0 to –15.2; <i>P</i><0.001).</p>
<p>Messerli et al¹⁵</p> <p>Study 1: Nifedipine 30 to 60 mg/day</p> <p>vs</p> <p>benazepril/amlodipine 10/5 or 20/5 mg</p> <p>Study 2: Amlodipine 5 to 10 mg/day</p> <p>vs</p> <p>benazepril/amlodipine 10/5 or 20/5 mg</p>	<p>Two DB, MC, RCT</p> <p>Patients 18 to 80 years of age with uncomplicated essential hypertension</p>	<p>N=1,079</p> <p>8 weeks</p>	<p>Primary: Change in DBP from baseline</p> <p>Secondary: Change from baseline in SBP and heart rate</p>	<p>Primary: Study 1 Significant reductions in DBP were observed with benazepril/amlodipine 10/5 and 20/5 mg (–9.4 and –9.7 mm Hg, respectively) compared to nifedipine 30 mg (–7.0 mm Hg; <i>P</i><0.05) but not nifedipine 60 mg (–8.5; <i>P</i>>0.05).</p> <p>Study 2 Benazepril/amlodipine 10/5 (–8.9 mm Hg) and 20/5 mg (–9.1 mm Hg) produced significantly greater reductions in DBP than amlodipine 5 mg (–6.8 mm Hg; <i>P</i><0.05) but not amlodipine 10 mg (–8.7 mm Hg; <i>P</i>>0.05).</p> <p>Secondary: Study 1 Significant reductions in SBP were observed with benazepril/amlodipine 20/5 mg (–11.6 mm Hg) compared to nifedipine 30 mg (–7.9 mm Hg; <i>P</i><0.05).</p> <p>Significantly less edema was reported with combination therapies (3.1 to 3.8%; <i>P</i>≤0.001) compared to nifedipine 60 mg (15.5%; <i>P</i>=0.008) but not nifedipine 30 mg (5.4%).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Study 2 Significant reductions in SBP were observed with benazepril/amlodipine 20/5 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.</p> <p>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%).</p>
<p>Jamerson et al¹⁶</p> <p>Benazepril/amlodipine 20/5 to 20/10 mg/day</p> <p>vs</p> <p>amlodipine 5 to 10 mg/day</p>	<p>DB, MC, PG, RCT</p> <p>Men and women 18 to 80 years of age with stage 2 hypertension</p>	<p>N=364</p> <p>12 weeks</p>	<p>Primary: Percentage of patients with SBP reduction ≥ 25 mm Hg (if baseline <180 mm Hg) or ≥ 32 mm Hg (if baseline ≥ 180 mm Hg)</p> <p>Secondary: Percentage of patients with DBP reduction ≥ 15 mm Hg (if baseline <110 mm Hg) or ≥ 20 mm Hg (if baseline ≥ 110 mm Hg), percentage of patients meeting goal of 140/90 and $\leq 130/85$ mm Hg, mean reduction in SBP and DBP and incidence of edema</p>	<p>Primary: Significantly more patients on combination therapy (74.2%) met the primary end point than patients on amlodipine monotherapy (53.9%; $P<0.0001$). The time by which 50% of patients attained the primary end point was four weeks shorter among patients randomized to combination therapy compared to those randomized to monotherapy ($P<0.0001$).</p> <p>Secondary: Significantly more patients on combination therapy met the DBP end point than patients on amlodipine monotherapy (67.0 vs 48.3%; $P=0.0003$).</p> <p>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 patients on amlodipine monotherapy.</p> <p>Significantly more patients on combination therapy met the BP goal of $<140/90$ mm Hg than patients on amlodipine monotherapy (61.0 vs 43.3%; $P=0.0007$).</p> <p>Significantly more patients on combination therapy met the BP goal of $<130/85$ mm Hg than patients on amlodipine monotherapy (35.7 vs 19.1%; $P=0.0004$).</p> <p>The incidence of peripheral edema was significantly higher in the amlodipine monotherapy group (23.3 vs 12.6%; $P=0.0102$).</p> <p>There was no significant difference in the incidence of other adverse events.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Neutel et al¹⁷ SELECT</p> <p>Benazepril/amlodipine 20/5 mg/day</p> <p>vs</p> <p>amlodipine 5 mg/day</p> <p>vs</p> <p>benazepril 20 mg/day</p>	<p>DB, RCT</p> <p>Patients with stage 2 systolic hypertension</p>	<p>N=443</p> <p>8 weeks</p>	<p>Primary: Reduction in SBP, proportion of patients achieving BP control</p> <p>Secondary: Not reported</p>	<p>Primary: Significantly greater SBP reductions were achieved with combination therapy compared to amlodipine or benazepril monotherapy ($P<0.0001$).</p> <p>Significantly more patients on combination therapy met BP goals than on monotherapy ($P<0.0001$).</p> <p>No significant difference was noted in the incidence of adverse events. Adverse events were low in all three treatment arms, with less peripheral edema in the combination group than in the amlodipine-treated group.</p> <p>Secondary: Not reported</p>
<p>Kuschnir et al¹⁸</p> <p>Benazepril 20 mg/day and amlodipine 5 mg/day</p> <p>vs</p> <p>amlodipine 5 mg/day</p> <p>vs</p> <p>benazepril 20 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Men and women 21 to 80 years of age with uncomplicated primary hypertension</p>	<p>N=308</p> <p>8 weeks</p>	<p>Primary: Reduction in mean sitting DBP, SBP and percentage of patients with DBP <90 mm Hg or a ≥ 10 mm Hg reduction</p> <p>Secondary: Not reported</p>	<p>Primary: All treatment groups significantly reduced mean sitting DBP compared to placebo ($P<0.001$).</p> <p>Combination therapy 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.</p> <p>Combination therapy 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).</p> <p>Significantly more patients on combination therapy reached DBP <90 mm Hg or a ≥ 10 mm Hg reduction (87.0%; $P\leq 0.005$) compared to amlodipine (67.5%) and benazepril (53.3%) monotherapy.</p> <p>Adverse events considered to be drug related occurred in 15.6% of patients receiving combination therapy, 24.7% of patients receiving amlodipine monotherapy, 6.5% of patients on benazepril monotherapy and 11.7% of patients on placebo (no P values reported).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Chrysant et al¹⁹</p> <p>Benazepril 40 mg and amlodipine 10 mg daily for 6 weeks</p> <p>vs</p> <p>benazepril 40 mg and amlodipine 10 mg daily for 2 weeks with forced titration to 40 and 20 mg daily for 4 weeks</p> <p>vs</p> <p>amlodipine 10 mg/day for 6 weeks</p>	<p>DB, MC, RCT</p> <p>Men and women ≥18 years of age with mean sitting DBP ≥95 mm Hg not adequately controlled with amlodipine 10 mg/day monotherapy</p>	<p>N=812</p> <p>6 weeks</p>	<p>Primary: Reduction in mean sitting DBP and SBP, reductions in ambulatory BP, successful response (mean sitting DBP <90 mm Hg or decrease of ≥10 mm Hg from baseline), safety</p> <p>Secondary: Not reported</p>	<p>Primary: Treatment with benazepril 40 mg and amlodipine 10 and benazepril 20 mg and amlodipine 10 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 to monotherapy (6.6/8.5 mm Hg; <i>P</i><0.0001).</p> <p>Benazepril 40 mg and amlodipine 10 mg and benazepril 40 mg and amlodipine 20 mg decreased ambulatory SBP and DBP by 9.9/6.7 and 7.4/5.2 mm Hg, respectively, compared to monotherapy (<i>P</i><0.0001).</p> <p>Both combination therapy groups resulted in more responders than monotherapy (74 and 65 vs 54%; <i>P</i><0.0001 and <i>P</i><0.0085, respectively). Combination therapy had significantly greater reductions in sitting SBP (–17 mm Hg; <i>P</i><0.0001) compared to amlodipine monotherapy (–5 mm Hg).</p> <p>The incidence of pedal edema was lower but not significantly different in the combination therapy groups compared to monotherapy (4.5, 5.5 vs 9.2%, respectively; <i>P</i>=NS). No significant metabolic side effects were noted among the combination therapy groups.</p> <p>Secondary: Not reported</p>
<p>Chrysant²⁰</p> <p>Benazepril 40 mg and amlodipine 5 mg daily for 4 weeks with forced titration to 40 and 10 mg/day for an additional 4 weeks</p> <p>vs</p> <p>benazepril 40 mg/day for 8 weeks</p>	<p>DB, RCT</p> <p>Men and women (mean age 53 years) with mean sitting DBP ≥95 mm Hg not adequately controlled with benazepril 40 mg/day monotherapy</p>	<p>N=329</p> <p>8 weeks</p>	<p>Primary: Reduction in mean sitting DBP and SBP, reduction in standing DBP and SBP, and change in heart rate, safety</p> <p>Secondary: Not reported</p>	<p>Primary: Combination therapy had significantly greater reductions in sitting SBP (–17 mm Hg; <i>P</i><0.0001) compared monotherapy (–5 mm Hg).</p> <p>Combination therapy had significantly greater reductions in sitting DBP (–14 mm Hg; <i>P</i><0.0001) compared to monotherapy (–7 mm Hg).</p> <p>Combination therapy had significantly greater reductions in standing SBP (–17 mm Hg; <i>P</i><0.0001) compared to monotherapy (–6 mm Hg).</p> <p>Combination therapy had significantly greater reductions in standing DBP (–14 mm Hg; <i>P</i><0.0001) compared to monotherapy (–7 mm Hg).</p> <p>No significant differences in heart rate were observed (<i>P</i>>0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>No significant differences in adverse events were reported ($P>0.05$).</p> <p>Secondary: Not reported</p>
<p>Fogari et al²¹</p> <p>Benazepril 10 mg and amlodipine 2.5 or 5 mg daily</p> <p>vs</p> <p>benazepril 10 mg/day</p>	<p>DB, MC, PC, RCT</p> <p>Men and women 24 to 73 years of age (mean 55 years) with hypertension inadequately controlled with ACE inhibitor monotherapy</p>	<p>N=448</p> <p>8 weeks</p>	<p>Primary: Reduction in mean sitting DBP</p> <p>Secondary: Reduction in sitting SBP, standing DBP and SBP, and percentage of patients with DBP <90 mm Hg (deemed excellent response) or a ≥ 10 mm Hg reduction (deemed good response)</p>	<p>Primary: Significantly greater reductions in sitting DBP were observed with benazepril 10 mg and amlodipine 2.5 mg (-5.3 mm Hg, 97.5% CI, -8.3 to -2.4; $P=0.0001$) and benazepril 10 mg and amlodipine 5 mg (-4.5 mm Hg, 97.5% CI, -7.4 to -1.6; $P=0.0006$) compared to benazepril monotherapy.</p> <p>Secondary: Significantly greater reductions in sitting SBP were seen with benazepril 10 mg and amlodipine 2.5 mg (-7.9 mm Hg, 97.5% CI, -12.3 to -3.5; $P=0.0001$) and benazepril 10 mg and amlodipine 5 mg (-7.9 mm Hg, 97.5% CI, -12.2 to -3.6; $P=0.0000$) compared to benazepril monotherapy.</p> <p>Significantly greater reductions in standing DBP and SBP were also reported with the combination therapy compared to benazepril monotherapy ($P\leq 0.001$).</p> <p>Significantly more patients had excellent or good response with benazepril 10 mg and amlodipine 2.5 mg (69.2%; $P=0.0004$) and 10/5 mg (65.8%; $P=0.02$) compared to benazepril monotherapy (40.5%).</p> <p>Tolerability was good in the three treatment groups and no significant abnormal laboratory data was detected.</p>
<p>Hilleman et al²²</p> <p>Benazepril/amlodipine</p> <p>vs</p> <p>9 monotherapies (atenolol, HCTZ, captopril, enalapril, lisinopril, amlodipine,</p>	<p>MA of RCT (published between January 1985 and January 1998) of first-line monotherapies and the fixed-dose combination</p> <p>Patients with mild-to-</p>	<p>82 studies enrolling ≥ 20 patients (total N not reported)</p> <p>≥ 4 weeks</p>	<p>Primary: Absolute change in supine DBP from baseline</p> <p>Secondary: Percent of patients who achieved BP control, safety</p>	<p>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, benazepril/amlodipine, atenolol, lisinopril, and verapamil showed the greatest BP effect.</p> <p>Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5 to 79.0%, with benazepril/amlodipine (74.3%) and lisinopril (79.0%) showing the highest percentage control ($P=0.096$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diltiazem, nifedipine and verapamil)	moderate essential hypertension			<p>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 to nifedipine ($P=0.030$).</p> <p>Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem ($P=0.002$). Although benazepril/amlodipine 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.</p>
<p>Bakris et al²³ GUARD</p> <p>Benazepril/amlodipine</p> <p>vs</p> <p>benazepril/HCTZ</p> <p>Doses were not specified.</p>	<p>DB, RCT</p> <p>Hypertensive, albuminuric type 2 diabetic patients, mean age 58 years randomized to receive either initial fixed-dose combination product</p>	<p>N=322</p> <p>52 weeks</p>	<p>Primary: Change in urinary albumin:creatinine ratio after one year of initial treatment with either fixed-dose combination, BP reductions</p> <p>Secondary: Proportion who progressed to overt diabetic nephropathy, safety</p>	<p>Primary: Both combinations significantly reduced the urinary albumin:creatinine ratio compared to baseline ($P<0.0001$). The median percent change was -72.1% for benazepril/HCTZ and -40.5% for benazepril/amlodipine ($P<0.0001$).</p> <p>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 amlodipine-based arm than in the HCTZ-based arm; however, significance in favor of the amlodipine based arm was observed only for DBP (SBP, -20.5 vs -18.8; $P=0.19$; DPB, -13.1 vs -9.97; $P=0.02$).</p> <p>A greater proportion of patients who had microalbuminuria at baseline and treated with benazepril/HCTZ compared to benazepril/amlodipine attained normalization of the urinary albumin:creatinine ratio, defined as <30 mg/g (69.2 vs 47.8%; $P=0.0004$).</p> <p>Secondary: The percentage of patients progressing to overt proteinuria was similar for both groups.</p> <p>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 benazepril/amlodipine 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</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Jamerson et al²⁴ ACCOMPLISH</p> <p>Benazepril/amlodipine 40/5 to 40/10 mg/day (forced titration after one month on benazepril/amlodipine 20/5 mg)</p> <p>vs</p> <p>benazepril/HCTZ 40/12.5 to 40/25 mg/day (forced titration after one month on benazepril/HCTZ 20/12.5 mg)</p>	<p>DB, MC, RCT</p> <p>Men and women >60 years of age with hypertension and at high risk for cardiovascular events (history of coronary events, MI, revascularization, or stroke; impaired renal function; peripheral arterial disease, left ventricular hypertrophy; or diabetes)</p>	<p>N=11,506</p> <p>5 years; study was terminated early at a mean of 30 months treatment exposure because observed difference between the groups exceeded pre-specified boundary</p>	<p>Primary: Time to first event (composite of cardiovascular event and death from cardiovascular causes)</p> <p>Secondary: Composite of cardiovascular events (the primary endpoint excluding fatal events) and composite of death from cardiovascular disease, nonfatal stroke and nonfatal MI</p>	<p>(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 <i>P</i> value reported).</p> <p>Primary: The primary endpoint occurred in 9.6% of patients in the benazepril/amlodipine group and 11.8% of patients in the benazepril/HCTZ group, representing a relative risk reduction of 11.8% (HR, 0.8; <i>P</i><0.001).</p> <p>Secondary: The secondary endpoint of cardiovascular events occurred in 8.6% of patients in the benazepril/amlodipine group and 10.3% in the benazepril/HCTZ, representing a relative risk reduction of 17.4% (HR, 0.83; <i>P</i>=0.002). The occurrence of the secondary composite endpoint of death from cardiovascular disease, nonfatal stroke and nonfatal MI was 5.0% in the benazepril/amlodipine group and 6.3% in the benazepril/HCTZ group, representing a relative risk reduction of 21.2% (HR, 0.79; <i>P</i>=0.002).</p> <p>Other prespecified endpoints of fatal and nonfatal MI, coronary revascularization procedures, rates of hospitalization adjudicated for congestive heart failure all favored benazepril/amlodipine.</p> <p>Adverse reactions were similar between the two groups with the most common being dizziness, peripheral edema and dry cough.</p>
<p>Bakris et al²⁵ ACCOMPLISH</p> <p>Benazepril/amlodipine 40/5 to 40/10 mg/day (forced titration after one month on benazepril/amlodipine 20/5 mg)</p> <p>vs</p> <p>benazepril/HCTZ 40/12.5 to 40/25 mg/day</p>	<p>Prespecified subanalysis of ACCOMPISH</p> <p>Men and women >60 years of age with hypertension and at high risk for cardiovascular events (history of coronary events, MI, revascularization, or stroke; impaired renal</p>	<p>N=11,482</p> <p>Mean treatment duration 2.9 years</p>	<p>Primary: Time to first event of doubling of serum creatinine concentration or end stage renal disease (defined as eGFR <15 mL/min/1.73 m² or need for chronic dialysis)</p> <p>Secondary:</p>	<p>Primary: There were fewer chronic kidney disease events in the benazepril/amlodipine group (2.0% of patients) compared to the benazepril/HCTZ group (3.7%; HR, 0.52; 95% CI, 0.41 to 0.65, <i>P</i><0.0001).</p> <p>Secondary: The composite endpoint of progression of chronic kidney disease and all-cause mortality was lower in the benazepril/amlodipine group (6.0%) compared to the benazepril/HCTZ group (8.1%; HR, 0.73; 95% CI, 0.64 to 0.84; <i>P</i><0.0001). There was a slower decline in eGFR in the benazepril/amlodipine group compared to the benazepril/HCTZ group (-0.88 vs -4.22 mL/min/1.73 m²; <i>P</i>=0.01). Of the patients with baseline microalbuminuria, there was a reduction in the urinary albumin:creatinine in the benazepril/HCTZ group of -63.8%</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(forced titration after one month on benazepril/HCTZ 20/12.5 mg)	function; peripheral arterial disease, left ventricular hypertrophy; or diabetes)		Progression of chronic kidney disease plus death, change in albuminuria, and change in eGFR	(median change) compared to a median change of -29.0% in the benazepril/amlodipine group ($P<0.0001$). There was a higher percentage of patients reporting peripheral edema in the benazepril/amlodipine group compared to the benazepril/HCTZ group ($P<0.0001$).
Weber et al ²⁶ ACCOMPLISH Benazepril/amlodipine 40/5 to 40/10 mg/day (forced titration after one month on benazepril/amlodipine 20/5 mg) vs benazepril/HCTZ 40/12.5 to 40/25 mg/day (forced titration after one month on benazepril/HCTZ 20/12.5 mg)	Prespecified subanalysis of ACCOMPISH Men and women >60 years of age with hypertension and at high risk for cardiovascular events (history of coronary events, MI, revascularization, or stroke; impaired renal function; peripheral arterial disease, left ventricular hypertrophy; or diabetes) (Subanalysis of patients with diabetes)	N=6,946 Mean treatment duration 29.7 months for benazepril/amlodipine group and 29.5 months for benazepril/HCTZ group	Primary: Primary: Time to first event (composite of cardiovascular event and death from cardiovascular causes) Secondary: Composite of cardiovascular events (the primary endpoint excluding fatal events) and composite of death from cardiovascular disease, nonfatal stroke and nonfatal MI	Primary: The primary endpoint occurred in 8.8% of diabetic patients in the benazepril/amlodipine group and 11.0% in the benazepril/HCTZ group (HR, 0.79; $P=0.003$; NNT, 46). In high risk diabetic patients, 13.6% of patients in the benazepril/amlodipine group and 17.3% in the benazepril/HCTZ group (HR, 0.77; $P=0.007$; NNT, 28). Secondary: Due to early termination, the study had limited power to detect differences in the diabetic subgroups. Peripheral edema was higher in the benazepril/amlodipine group compared to the benazepril/HCTZ group.
Malacco et al ²⁷ Benazepril/amlodipine 10/5 mg/day vs captopril/HCTZ 50/25	DB, MC, RCT Patients with mild-to-moderate arterial hypertension (sitting DBP >95 mm Hg and/or SBP >160 mm Hg) inadequately	N=397 12 weeks	Primary: Reduction in DBP and SBP Secondary: Percentage of patients responding to therapy (DBP	Primary: Significantly lower sitting DBP (-2.7 mm Hg; $P<0.001$) and SBP (-3.7 mm Hg; $P<0.001$) were achieved with benazepril/amlodipine compared to captopril/HCTZ. Secondary: Significantly more benazepril/amlodipine patients responded to therapy (94.8%) compared to captopril/HCTZ patients (86.0%; $P=0.004$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day	controlled by monotherapy with an ACE inhibitor, calcium-channel blocking agent or diuretic		<90 mm Hg, a reduction in DBP ≥10 mm Hg or SBP ≥20 mm Hg, or SBP <150 mm Hg)	No differences in adverse events were reported between the two treatment groups.
<p>Kereiakes et al²⁸</p> <p>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</p> <p>vs</p> <p>olmesartan 20 mg/day for 2 weeks, then 40 mg/day for 2 weeks then olmesartan/HCTZ 40/12.5 mg/day for 4 weeks increased to 40/25 mg for 4 weeks</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients with stage 2 hypertension</p>	<p>N=190</p> <p>12 weeks</p>	<p>Primary: Change in mean seated SBP at the end of week 12</p> <p>Secondary: DBP at the end of week 12, percent of patients attaining BP goals of <140/90, <130/85 and <130/80 mm Hg</p>	<p>Primary: Patients treated with olmesartan/HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril plus 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).</p> <p>Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan/HCTZ compared to benazepril plus amlodipine at week 12 ($P=0.056$).</p> <p>The percentage of patients achieving goal rates at the end of the study for olmesartan/HCTZ and benazepril plus 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.</p> <p>Both treatments were well tolerated.</p>
<p>McInnes et al²⁹</p> <p>Lisinopril/HCTZ 10/12.5 mg/day</p> <p>vs</p> <p>candesartan/HCTZ 8/12.5 mg/day</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 20 to 80 years of age with mild-to-moderate hypertension on prior antihypertensive monotherapy</p>	<p>N=355</p> <p>26 weeks</p>	<p>Primary: Mean changes in DBP</p> <p>Secondary: Mean changes in SBP and heart rate, proportion of responders and</p>	<p>Primary: Changes in mean sitting DBP did not differ significantly between the groups (mean difference, 0.5 mm Hg; $P=0.20$).</p> <p>Secondary: No significant differences between the groups were reported for mean sitting SBP, heart rate, proportion of responders and controlled patients.</p> <p>Both regimens were well tolerated but a greater percentage of those in the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			controlled patients, safety	lisinopril based 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 based group compared to the candesartan based group.
<p>Pepine et al³⁰ INVEST</p> <p>Verapamil SR 240 mg/day (step 1), then trandolapril added if needed (step 2), then doses of both increased (step 3), then HCTZ added (step 4); calcium antagonist strategy group (CAS)</p> <p>vs</p> <p>atenolol 50 mg/day (step 1), then HCTZ added if needed (step 2), then doses of both increased (step 3), then trandolapril added (step 4); non-calcium antagonist strategy group (NCAS)</p> <p>Trandolapril was recommended for all patients with heart failure, diabetes, or renal insufficiency.</p>	<p>MC, OL, RCT</p> <p>Men and women with essential hypertension (as defined by JNC VI) and CAD, mean age 66 years</p>	<p>N=22,576</p> <p>24 months</p>	<p>Primary: First occurrence of death (all cause), nonfatal MI or stroke</p> <p>Secondary: Cardiovascular death, angina, cardiovascular hospitalization, angina, BP control (JNC VI goals SBP/DBP <140/90 or <130/85 mm Hg if diabetic or renal impairment), safety</p>	<p>Primary: At 24 months, in the CAS subgroup, 81.5% of patients were taking verapamil SR, 62.9% trandolapril and 43.7% HCTZ. In the NCAS, 77.5% of patients were taking atenolol, 60.3% HCTZ and 52.4% trandolapril.</p> <p>After a follow-up of 61,835 patient-years (mean, 2.7 years/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; $P=0.57$).</p> <p>Secondary: There was no significant difference in the rate of cardiovascular death ($P=0.94$) or cardiovascular hospitalization ($P=0.59$) between the two treatment groups.</p> <p>At 24 months, angina episodes decreased in both groups, but the mean frequency was lower in the CAS group (0.77 episodes/week) compared to the NCAS group (0.88 episodes/week; $P=0.02$).</p> <p>Two-year BP control was similar between groups. The JNC VI BP 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.</p> <p>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 $P\leq 0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Pepine et al³¹ INVEST (see above)</p> <p>Verapamil SR 240 mg/day (step 1), then trandolapril added if needed (step 2), then doses of both increased (step 3), then HCTZ added (step 4)</p> <p>vs</p> <p>atenolol 50 mg/day (step 1), then HCTZ added if needed (step 2), then doses of both increased (step 3), then trandolapril added (step 4)</p>	<p>Post hoc analysis of INVEST (see above)</p> <p>Men and women with essential hypertension (as defined by JNC VI) and CAD, mean age 66 years</p>	<p>N=22,576</p> <p>24 months</p>	<p>Primary: Risk for adverse outcome associated with baseline factors, follow-up BP and drug treatments</p> <p>Secondary: Not reported</p>	<p>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.</p> <p>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.</p> <p>Secondary: Not reported</p>
<p>Brunner et al³² INVEST (see above)</p> <p>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 BP goals.</p>	<p>Post hoc analysis of INVEST (see above)</p> <p>Men and women with essential hypertension (as defined by JNC VI) and CAD, mean age 66 years</p>	<p>N=1,832 (subset of INVEST)</p> <p>24 months</p>	<p>Primary: Factors influencing BP response to trandolapril add-on therapy</p> <p>Secondary: Not reported</p>	<p>Primary: Trandolapril decreased mean unadjusted SBP and DBP by –9.1 and –4.1 mm Hg, respectively. The percentage of patients with BP under control (<140/90 mm Hg) increased from 6.7 to 41.3% ($P<0.0001$).</p> <p>Adjusted BP 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.</p> <p>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 BP control similar to the other ethnic groups.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Karlberg et al ³³ Trandolapril 2 mg/day vs verapamil 240 mg/day vs trandolapril/verapamil 2/180 mg/day	DB, MC, PRO, RCT, XO Patients 20 to 80 years of age with uncomplicated primary hypertension (sitting DBP between 95 and 115 mm Hg)	N=226 2 months	Primary: Change in BP and rate pressure product Secondary: Predictive value of plasma concentrations of active renin regarding the BP response to the different treatment regimens, safety	Not reported Primary: The mean fall in BP was significantly greater with combination therapy (20/15 mm Hg; $P<0.00054$), as compared to both trandolapril (14/11 mm Hg) and verapamil (13/11 mm Hg) monotherapy. The difference between verapamil and trandolapril was not significant. Rate pressure product decreased significantly more with the combination ($P<0.001$) therapy than with trandolapril or verapamil monotherapy. Secondary: There was a significant positive correlation between BP fall and plasma concentrations of active renin (e.g., the higher the initial active renin, the better the BP response to trandolapril monotherapy [$P<0.045$ for SBP and $P<0.004$ for DBP]). No relationships were found for either verapamil monotherapy or combination therapy. All treatments were well tolerated and safe.
Ruggenenti et al ³⁴ BENEDICT Trandolapril 2 mg/day vs verapamil SR 240 mg/day vs trandolapril/verapamil SR 2/180 mg/day 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 $\mu\text{g}/\text{minute}$)	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, BP, adverse events	Primary: The primary outcome was reached in 5.7% of patients receiving combination therapy vs 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 combination therapy and placebo ($P=0.01$). Secondary: The primary outcome was reached in 6.0% of patients receiving trandolapril, 11.9% of patients receiving verapamil and 10.0% of patients 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 ($P=0.54$). Combination therapy and trandolapril monotherapy 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>patients receiving combination therapy, 139/81 mm Hg for trandolapril monotherapy, 141/82 mm Hg for verapamil monotherapy and 142/83 mm Hg for placebo. The comparison was significant ($P \leq 0.002$) between combination therapy or trandolapril monotherapy vs placebo, but not for verapamil monotherapy vs placebo.</p> <p>Serious adverse events were similar in all treatment groups.</p>
<p>Cifkova et al³⁵</p> <p>Trandolapril/verapamil SR 2/180 mg/daily (TV)</p> <p>vs</p> <p>captopril/HCTZ 50/25 mg/daily (CH)</p> <p>After 16 weeks, patients were switched to the other fixed combination for an additional 16 weeks.</p>	<p>AC, OL, RCT, XO</p> <p>Caucasian patients aged 18 to 75 years with mild-to-moderate essential hypertension (SBP 140 to 209 mm Hg and DBP 90 to 119 mm Hg)</p>	<p>N=100</p> <p>8 months</p>	<p>Primary: LDL-C</p> <p>Secondary: Other lipid parameters (HDL-C, TC, triglycerides, apolipoproteins AI and B, lipoprotein(a)), BP parameters</p>	<p>Primary: LDL-C was not significantly different between the two treatment groups ($P=0.909$).</p> <p>Secondary: All secondary lipid parameters remained unaltered except for HDL-C which was significantly higher with TV (1.39 vs 1.35 mmol/L; $P<0.03$).</p> <p>Serum potassium declined while uric acid and glucose increased on CH (all $P<0.001$).</p> <p>While there were no significant differences with respect to adjusted mean DBP, adjusted mean SBP was slightly higher on treatment with TV 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 ($P=0.02$) 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 (TV, 56% vs CH, 46%; $P=NS$). Heart rate was significantly lower in the TV group than the CH group (treatment differences ranged from 2.8 to 4.5 beats/minute; all $P \leq 0.001$).</p>

Drug regimen abbreviations: HCTZ=hydrochlorothiazide, SR=sustained-release

Study abbreviations: AC=active comparator, DB=double-blind, DD=double dummy, 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, XO=cross over

Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, BP=blood pressure, CAD=coronary artery disease, CI=confidence interval, DBP=diastolic blood pressure, eGFR=estimated glomerular filtration rate, HDL-C=high-density lipoprotein cholesterol, HR=hazard ratio, JNC=Joint National Committee, LDL-C=low-density lipoprotein cholesterol, MI=myocardial infarction, mm Hg=millimeters of mercury, NNT=number needed to treat, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TIA=transient ischemic attack

Special Populations

Table 5. Special Populations⁴⁻¹⁴

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Benazepril/ amlodipine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment is required in patients with creatinine clearance > 30 mL/min/1.73 m ² . Not recommended in patients with severe renal impairment.	Dosage adjustment is required; initial dose of amlodipine is 2.5 mg.	D	Yes/ unknown
Benazepril/ HCTZ	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Use with caution.	Use with caution.	D	Yes
Captopril/HCTZ	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Use with caution.	Use with caution.	C (first trimester) D (second and third trimesters)	Yes
Enalapril/HCTZ	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Use with caution.	Use with caution.	C (first trimester) D (second and third trimesters)	Yes
Fosinopril/ HCTZ	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Use with caution.	Use with caution.	C (first trimester) D (second and third trimesters)	Yes

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Lisinopril/HCTZ	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment is required in patients with creatinine clearance >30 mL/min/1.73 m ² . Not recommended in patients with severe renal impairment.	Use with caution.	C (first trimester) D (second and third trimesters)	Unknown/ yes
Moexipril/HCTZ	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment is required in patients with creatinine clearance >40 mL/min/1.73 m ² . Not recommended in patients with severe renal impairment.	Not studied in hepatic dysfunction.	C (first trimester) D (second and third trimesters)	Unknown/ yes
Quinapril/HCTZ	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment is required in patients with creatinine clearance >30 mL/min/1.73 m ² . Not recommended in patients with severe renal impairment.	Use with caution.	C (first trimester) D (second and third trimesters)	Yes
Trandolapril/ verapamil	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C (first trimester) D (second and third trimesters)	Yes

HCTZ=hydrochlorothiazide

Adverse Drug Events

The adverse drug event profile of the combination angiotensin-converting enzyme 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.⁸ Adverse events presented in table 6 are those reported in the prescribing information for the combination products. These adverse effects may differ from those reported in each individual agent, which are covered in their respective product reviews.

Table 6. Adverse Drug Events (%)⁵⁻¹⁴

Adverse Event	Benazepril/ Amlodipine	Benazepril/ HCTZ	Captopril/ HCTZ	Enalapril/ HCTZ	Fosinopril/ HCTZ	Lisinopril/ HCTZ	Moexipril/ HCTZ	Quinapril/ HCTZ	Trandolapril/ Verapamil
Cardiovascular									
Angina	-	-	0.2 to 0.3	-	-	-	-	-	-
Atrioventricular block	-	-	-	-	-	-	-	-	3.9
Bradycardia	-	-	-	-	-	-	-	-	1.8
Cardiac arrest	-	-	✓	-	-	-	-	-	-
Cerebrovascular accident	-	-	✓	-	-	-	-	-	-
Chest pain	-	-	1	-	0.5 to <2.0	-	>1	1	2.2
Hypotension	-	0.6	✓	-	-	1.4	>1	-	-
Myocardial infarction	-	-	0.2 to 0.3	-	-	-	-	-	-
Orthostatic hypotension	-	0.3 to 3.5	✓	2.3	1.8	0.5	<1	≥0.5 to <1.0	-
Palpitations	-	-	1	0.5 to 2.0	-	-	-	≥0.5 to <1.0	-
Tachycardia	-	-	1	-	-	-	-	-	-
Central Nervous System									
Depression	-	-	✓	-	-	-	-	-	-
Dizziness	1.3	6.3	-	8.6	3.2	7.5	1.4	4.8	3.1
Fatigue	✓	5.2	-	3.9	3.9	3.7	1	2.9	2.8
Headache	2.2	3.1	-	5.5	7	5.2	>1	6.7	8.9
Insomnia	✓	✓	-	0.5 to 2.0	-	-	-	1.2	-
Peripheral edema	-	-	-	-	-	-	-	-	-
Somnolence/drowsiness	-	1.2	✓	-	-	-	-	1.2	-
Dermatologic									
Flushing	✓	0.3 to 1.0	0.2 to 0.5	✓	0.5 to <2.0	-	-	-	≥0.3 to <1.0
Pruritus	-	-	2	-	-	-	-	✓	-
Rash	✓	-	4 to 7	✓	0.5 to <2.0	1.2	>1	-	≥0.3 to <1.0
Stevens-Johnson syndrome	✓	✓	✓	✓	✓	-	-	✓	✓
Gastrointestinal									
Abdominal pain	-	-	-	-	-	-	-	1.7	-

Adverse Event	Benazepril/ Amlodipine	Benazepril/ HCTZ	Captopril/ HCTZ	Enalapril/ HCTZ	Fosinopril/ HCTZ	Lisinopril/ HCTZ	Moexipril/ HCTZ	Quinapril/ HCTZ	Trandolapril/ Verapamil
Constipation	-	-	-	-	-	-	-	-	3.3
Diarrhea	✓	0.3 to 1.0	✓	2.1	0.5 to <2.0	2.5	>1	1.4	1.5
Dysgeusia	-	-	2 to 4	-	-	-	-	-	-
Dyspepsia	-	-	✓	-	-	-	-	-	-
Hepatitis	-	-	✓	-	-	-	-	-	-
Increased liver enzymes	-	-	-	-	-	-	-	-	2.8
Jaundice	✓	✓	✓	✓	✓	-	<1	✓	✓
Nausea	✓	1.4	-	2.5	✓	2.2	>1	✓	1.5
Pancreatitis	-	-	✓	-	-	-	-	-	-
Genitourinary									
Decreased libido	-	-	✓	-	✓	-	-	-	-
Impotence	✓	1.2	-	2.2	-	1.2	>1	≥0.5 to <1.0	≥0.3 to <1.0
Oliguria	-	-	0.1 to 0.2	-	-	-	-	-	-
Musculoskeletal									
Arthralgia	-	-	-	-	-	-	-	-	1.7
Back pain	-	-	-	-	-	-	-	-	1.1
Hypertonia	-	1.5	-	-	-	-	-	-	-
Muscle cramps	-	-	-	2.7	-	2	-	-	-
Musculoskeletal pain	-	-	-	-	2	-	-	-	1.1
Myalgia	-	-	✓	-	-	-	-	2.4	-
Respiratory									
Bronchitis	-	-	-	-	-	-	-	1.2	1.8
Cough	3.3	2.1	0.5 to 2.0	3.5	5.6	3.9	3	3.2	4.6
Dyspnea	-	-	-	-	-	-	-	-	1.3
Rhinitis	-	-	✓	-	-	-	-	2	-
Upper respiratory tract infection	-	-	-	-	2.3	2.2	>1	1.3	5.4
Miscellaneous									
Anemia	-	-	≤0.2	-	-	-	-	-	-
Angioedema	-	0.3	0.1	0.5 to 2.0	0.5 to <2.0	0.3 to 1.0	>1	0.1	-
Asthenia	-	-	✓	2.4	-	1.8	<1	≥0.5 to <1.0	-
Blurred vision	-	-	✓	-	-	-	-	-	-
Edema	2.1	-	-	-	-	-	-	-	≥0.3 to <1.0
Eosinophilia	-	-	✓	-	-	-	-	-	-
Fever	-	-	✓	-	-	-	-	-	-
Hyperkalemia	1.5	-	-	-	-	-	-	-	-

Adverse Event	Benazepril/ Amlodipine	Benazepril/ HCTZ	Captopril/ HCTZ	Enalapril/ HCTZ	Fosinopril/ HCTZ	Lisinopril/ HCTZ	Moexipril/ HCTZ	Quinapril/ HCTZ	Trandolapril/ Verapamil
Neutropenia	✓	-	✓	-	0.5 to <2.0	-	-	-	-
Syncope	-	-	✓	-	-	-	<1	-	-
Viral infection	-	-	-	-	-	-	-	1.9	-

HCTZ=hydrochlorothiazide

- Event not reported or incidence <1%.

✓ Percent not specified.

Contraindications/Precautions⁵⁻¹⁴

Angiotensin converting enzyme (ACE) inhibitors are contraindicated with patients with a history of angioedema. Hydrochlorothiazide is contraindication in patients who are anuric. Because of the verapamil component, trandolapril/verapamil is contraindicated in patients with severe left ventricular dysfunction, hypotension or cardiogenic shock, sick sinus syndrome, second or third degree atrioventricular block and patients with atrial flutter or atrial fibrillation and an accessory bypass.

Angioedema of the face, extremities, lips, tongue, glottis and larynx has been reported in patients treated with ACE inhibitors. Interstitial angioedema has also been reported.

ACE inhibitors and verapamil are associated with symptomatic hypotension. Agents containing these components should be used with caution in patients receiving other antihypertensive agents.

ACE inhibitors cause fetal and neonatal morbidity and death resulting in the black box warning outlined below. In the rare case that there is no alternative agent available, the mother should be apprised of the potential hazards and there should be additional monitoring of the fetus.

ACE inhibitors have been associated with changes in electrolytes including hyperkalemia. However, hydrochlorothiazide is associated with hypokalemia. In the combination agents containing hydrochlorothiazide, the effects on serum potassium may balance each other or manifest as either decreased or increased serum potassium.

In patients undergoing surgery or during anesthesia with agents that produce hypotension, ACE inhibitors can potentiate the hypotension. This hypotension can be corrected by volume expansion.

Captopril has been shown to cause agranulocytosis and bone marrow suppression. Insufficient data is available if other ACE inhibitors are associated with similar rates of bone marrow suppression.

ACE inhibitors may cause changes in renal function, especially in susceptible patients, such as those with severe congestive heart failure. In addition, loop diuretics are preferred over thiazide diuretics in patients with severe renal impairment. Thiazides may precipitate azotemia in such patients.

Thiazide diuretics have caused activation or exacerbation of systemic lupus erythematosus.

Increased frequency, duration, or severity of angina or acute myocardial infarction has developed, particularly in patients with severe obstructive coronary artery disease, at the start or dose increase of calcium channel blocker therapy.

Verapamil has been associated with elevation of liver transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin. In addition, rarely, ACE inhibitors have been associated with cholestatic jaundice that progresses to fulminant hepatic necrosis and sometimes death. Due to the extensive metabolism of amlodipine and verapamil in the liver, the combination products containing these agents should be used with caution in patients with hepatic impairment.

In patients with hypertrophic cardiomyopathy receiving verapamil, serious adverse events have been observed, including pulmonary edema/severe edema and death.

Black Box Warning: captopril/hydrochlorothiazide, enalapril/hydrochlorothiazide, fosinopril/hydrochlorothiazide, lisinopril/hydrochlorothiazide, moexipril/hydrochlorothiazide, quinapril/hydrochlorothiazide, trandolapril/verapamil⁴

WARNING

Use in Pregnancy

When used in pregnancy during the second and third trimesters, angiotensin-converting enzyme (ACE)
--

WARNING

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.

Black Box Warning: benazepril/amlodipine, benazepril/hydrochlorothiazide⁴

WARNING

Avoid Use in Pregnancy
When used in pregnancy, 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.

Drug Interactions

Table 7. Drug Interactions⁴⁻¹⁴

Drug	Interaction	Mechanism
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, trandolapril	Indomethacin	Indomethacin inhibits prostaglandin synthesis. The hypotensive effect of angiotensin-converting enzyme inhibitors may be reduced.
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, trandolapril	Lithium	Through an unknown mechanism, angiotensin-converting enzyme inhibitors may increase lithium levels which results in neurotoxicity.
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, trandolapril	Potassium-sparing diuretics (amiloride, spironolactone, triamterene)	Combining angiotensin-converting enzyme inhibitors and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high-risk patients (e.g., renal impairment).
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, trandolapril	Salicylates (aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate)	Salicylates inhibit prostaglandin synthesis. The hypotensive and vasodilator effects of the angiotensin-converting enzyme inhibitor may be reduced.
Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, trandolapril	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Angiotensin-converting enzyme inhibitors may temporarily increase insulin sensitivity and increase the risk of hypoglycemia.
Hydrochlorothiazide	Cisapride	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased due to electrolyte loss from thiazide diuretics.
Hydrochlorothiazide	Diazoxide	Hyperglycemia may occur with symptoms similar to diabetes. The mechanism is unknown.
Hydrochlorothiazide	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose the patient to digitalis-induced cardiac arrhythmias.
Hydrochlorothiazide	Dofetilide	Thiazide diuretics increase potassium excretion.

Drug	Interaction	Mechanism
		Hypokalemia may occur, increasing the risk of torsades de pointes. Coadministration of dofetilide and thiazide diuretics is contraindicated.
Hydrochlorothiazide	Lithium	Thiazide diuretics decrease the renal clearance of lithium which leads to increased serum lithium levels. Lithium toxicity has occurred.
Hydrochlorothiazide	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	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.
Verapamil	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	Buspirone	Verapamil may enhance the bioavailability of buspirone. The pharmacologic and adverse effects of buspirone may be increased.
Verapamil	Calcium salts	Calcium salts antagonize some of the effects of verapamil and the clinical effects and toxicities of verapamil may be reversed.
Verapamil	Carbamazepine	Verapamil appears to impair the hepatic metabolism of carbamazepine. Carbamazepine levels may increase, resulting in an increase in pharmacologic and toxic effects.
Verapamil	Charcoal	Charcoal will reduce the gastrointestinal absorption of orally administered verapamil and reduce its effectiveness or toxicity.
Verapamil	Cyclosporine	Verapamil may inhibit cyclosporine metabolism leading to increased cyclosporine levels and toxicity (e.g., nephrotoxicity). However, giving verapamil before cyclosporine may be nephroprotective. The interaction is typically observed within seven days of starting verapamil and may abate within one week after discontinuation.
Verapamil	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	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

Drug	Interaction	Mechanism
		contraindicated.
Verapamil	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	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	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	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	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	Prazosin	Verapamil can increase serum levels of prazosin through an unknown mechanism, causing increased sensitivity to prazosin-induced postural hypotension.
Verapamil	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	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.
Verapamil	Rifampin	First-pass hepatic metabolism of verapamil may be increased, resulting in lowered bioavailability and reduced effectiveness of oral verapamil.

Dosage and Administration

The usual dosing regimens for the combination angiotensin-converting enzyme (ACE) inhibitors are summarized in Table 8. Captopril/hydrochlorothiazide is the only combination ACE inhibitor Food and Drug Administration-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 8. Dosing and Administration⁵⁻¹⁴

Generic Name	Usual Adult Dosage	Usual Pediatric Dosage	Availability
Benazepril/ amlodipine	<u>Hypertension in patients not adequately controlled on monotherapy with either agent:</u> 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: 10/2.5 mg 10/5 mg 20/5 mg 20/10 mg 40/5 mg 40/10 mg
Benazepril/ HCTZ	<u>Hypertension:</u> Fixed-combination drug is not indicated for initial therapy; switch to 10/12.5 mg or 20/12.5 mg/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: 5/6.25 mg 10/12.5 mg 20/12.5 mg 20/25 mg
Captopril/ HCTZ	<u>Hypertension as either initial therapy or substituted for previously titrated doses of the individual products:</u> Initial: 25/15 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/HCTZ should not exceed 150/50 mg, respectively	Safety and efficacy in children have not been established.	Tablet: 25/15 mg 25/25 mg 50/15 mg 50/25 mg
Enalapril/ HCTZ	<u>Hypertension:</u> Fixed-combination drug is not indicated for initial therapy; initiate combination on 10/25 mg therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum, 4 tablets of 5/12.5 mg or 2 tablets of 10/25 mg	Safety and efficacy in children have not been established.	Tablet: 5/12.5 mg 10/25 mg
Fosinopril/ HCTZ	<u>Hypertension:</u> 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: 10/12.5 mg 20/12.5 mg
Lisinopril/ HCTZ	<u>Hypertension:</u> Fixed-combination drug is not indicated for initial therapy; initiate combination therapy on 10/12.5 or 20/12.5 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: 10/12.5 mg 20/12.5 mg 20/25 mg
Moexipril/ HCTZ	<u>Hypertension:</u> Fixed-combination drug is not indicated for initial therapy; initiate combination	Safety and efficacy in children have not been established.	Tablet: 7.5/12.5 mg 15/12.5 mg

Generic Name	Usual Adult Dosage	Usual Pediatric Dosage	Availability
	therapy on 7.5/12.5, 15/12.5 or 15/25 mg after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; maximum, moexipril/HCTZ 30/50 mg/day		15/25 mg
Quinapril/ HCTZ	<u>Hypertension:</u> Fixed-combination drug is not indicated for initial therapy; initiate combination therapy on 10/12.5 or 20/12.5 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: 10/12.5 mg 20/12.5 mg 20/25 mg
Trandolapril/ verapamil	<u>Hypertension:</u> 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 to 4 mg/day in 1 to 2 divided doses and for verapamil extended-release 120 to 480 mg/day in 1 to 2 divided doses)	Safety and efficacy in children have not been established.	Tablet, extended-release: 1/240 mg 2/180 mg 2/240 mg 4/240 mg

HCTZ=hydrochlorothiazide

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute: The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004) ³⁷	<ul style="list-style-type: none"> Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with another class (angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], β-blockers, calcium channel blockers) demonstrated to be beneficial in randomized controlled outcome trials. Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs or calcium channel blockers. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial 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 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

Clinical Guideline	Recommendation(s)
	<p>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.</p> <ul style="list-style-type: none"> • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), post-myocardial infarction (β-blockers, ACE inhibitors and aldosterone antagonists), high coronary disease risk (diuretics, ACE inhibitors, β-blockers and calcium channel blockers), diabetes (diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers), chronic kidney disease (ACE inhibitors and ARBs) and recurrent stroke prevention (diuretics and ACE inhibitors). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting calcium channel blockers 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 calcium channel blockers 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 microalbuminuria. • Patients with chronic kidney disease often require treatment with three 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 calcium channel blockers and diuretics. The incidence of ACE-inhibitor-induced angioedema is two to four times higher in African Americans. • Calcium channel blockers 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.
<p>World Health Organization/ International Society of Hypertension: 2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)³⁸</p>	<ul style="list-style-type: none"> • When used as monotherapy, a diuretic or a calcium channel blocker 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 calcium channel blockers), renal disease (ACE inhibitors and ARBs), post-myocardial infarction (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).
<p>European Society of Hypertension/ European Society of</p>	<ul style="list-style-type: none"> • In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which

Clinical Guideline	Recommendation(s)
<p>Cardiology: 2007 Guidelines for the Management of Hypertension (2007)³⁹, Reappraisal of Guidelines on Hypertension Management (2009)⁴⁰</p>	<p>must include a search for subclinical organ damage.</p> <ul style="list-style-type: none"> • In general, early introduction of blood pressure lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, is recommended. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs and calcium channel blockers), asymptomatic atherosclerosis (calcium channel blockers and ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers and ARBs), angina (calcium channel blockers and β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors and ARBs), permanent atrial fibrillation (β-blockers and nondihydropyridine calcium channel blockers), end stage renal disease/proteinuria (ACE inhibitors, ARBs and loop diuretics), metabolic syndrome (ACE inhibitors, ARBs and calcium channel blockers), diabetes (ACE inhibitors and ARBs), pregnancy (methyldopa, calcium channel blockers and β-blockers) and African American patients (calcium channel blockers and diuretics). • Available evidence justifies the use of aliskiren in hypertension, particularly in combination with other agents. • 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, consider medications which have different and complementary mechanisms of action, and that 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. <ul style="list-style-type: none"> • Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a diuretic with an ACE inhibitor, ARB or calcium channel blocker and an ACE inhibitor with a calcium channel blocker. • Avoid β-blocker/diuretic combination unless required for other reasons. • If triple therapy is needed, the most rational combination is a blocker of the rennin-angiotensin system, a calcium channel blocker and a diuretic at effective doses. • A β- or α-blocker may be included in a triple therapy approach depending on clinical circumstances. • Antihypertensive treatment is highly beneficial in elderly patients and treatment may be initiated with a thiazide diuretic, ACE inhibitor, calcium channel blocker, ARB or β-blocker. • Blood pressure lowering drugs should be continued or initiated in patients 80 years of age, starting with monotherapy and adding a second drug, if needed. The decision to treat should be made on an individual basis and patients should be carefully monitored.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Calcium channel blockers, ARBs and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. • Antihypertensive treatment should always be initiated in diabetic patients when blood pressure is 140/90 mm Hg or higher; however, there is evidence in favor of initiating treatment with high normal blood pressure. • The blood pressure goal of <130/80 mm Hg is not supported by outcome evidence from trials and is difficult for the majority of patients to achieve; therefore, its realistic to recommend only to pursue a sizeable blood pressure reduction without indicating a goal that is unproven. • In hypertensive diabetic patients, tight blood glucose control (glycosylated hemoglobin to 6.5%) is beneficial, particularly in combination with effective blood pressure control, on improving microvascular complications. Tight glucose control should not be pursued abruptly and patients should be monitored closely due to the increased risk of severe hypoglycemic episodes.
<p>National Institute for Health and Clinical Excellence/British Hypertension Society: Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)⁴¹</p>	<ul style="list-style-type: none"> • Initial therapy in patients ≥55 years of age should be a calcium channel blocker or a thiazide diuretic. • Initial therapy in patients <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 calcium channel blocker or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a calcium channel blocker or a diuretic should be added. • If three medications are required, a combination of calcium channel blocker, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.

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 or verapamil). All of the combination ACE inhibitors as well as their individual components are available generically. All of the combination ACE inhibitors are Food and Drug Administration (FDA) approved for the treatment of hypertension. Only captopril/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.³⁷⁻⁴¹ The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) states that most patients with stage 2 hypertension will require initial therapy with medications from two drug classes and recommends that thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy.³⁷ 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.⁴²⁻⁴⁵

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Avg # of Units/Day	Plan Cost \$	Avg \$/Rx
Lisinopril/HCT	630	1,143	84.54%	1.1	\$23,830.72	\$20.85
Amlodipine/benazepril	81	131	9.70%	1.1	\$23,974.57	\$183.01
Enalapril/HCT	25	45	3.33%	1.0	\$1,097.74	\$24.39
Benazepril/HCT	16	23	1.70%	1.3	\$814.67	\$35.42
Moexipril/HCT	3	6	0.44%	1.0	\$382.94	\$63.82
Quinapril/ HCT	2	3	0.22%	1.0	\$264.42	\$88.14
Lotrel	1	1	0.07%	1.0	\$421.87	\$421.87
Class Total:	NA	1,352	100%	1.1	\$50,786.93	\$37.56

Recommendations

In recognition of the following factors:

- The well-established role of the angiotensin converting enzyme inhibitors in the treatment of hypertension and other cardiovascular and renal diseases.
- The generic availability of all products within the class.

...it is recommended that no changes be made to the current Department of Vermont Health Access (DVHA) combination angiotensin-converting enzyme inhibitors approval criteria (see below).

ACE Inhibitor/Hydrochlorothiazide combinations:

- The patient has had a documented side effect, allergy, or treatment failure to all available preferred generic ACEI/Hydrochlorothiazide combination. If a medication has an AB rated generic, there must have been a trial of the generic formulation.

ACE Inhibitor/Calcium Channel Blocker combination:

- The patient has had a documented side effect, allergy, or treatment failure with a preferred ACEI/Calcium Channel Blocker combination. If a medication has an AB rated generic, the trial must be the generic formulation.

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