Therapeutic Class Overview
Angiotensin-Converting Enzyme (ACE) Inhibitors Single Entity Agents

Therapeutic Class

- **Overview/Summary:** The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[1,2] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[3] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase).[1] Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[1,3] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including ventricular hypertrophy, remodeling and myocyte apoptosis.[1,2] The ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator.[4] Evidence-based guidelines recognize the important role that ACE inhibitors play in the treatment of hypertension and other cardiovascular and renal diseases. With the exception of Epaned® (enalapril solution), all of the ACE inhibitors are available generically.

Table 1. Current Medications Available in Therapeutic Class[5-18]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Benazepril (Lotensin®*)	Hypertension	Tablet: 5 mg 10 mg 20 mg 40 mg	✔
Captopril (Capoten®*)	Diabetic nephropathy, heart failure, hypertension, left ventricular dysfunction post-myocardial infarction	Tablet: 12.5 mg 25 mg 50 mg 100 mg	✔
Enalapril (Vasotec®*, Epaned®)	Asymptomatic left ventricular dysfunction, heart failure, hypertension	Tablet: 2.5 mg 5 mg 10 mg 20 mg	✔
Enalaprilat*	Hypertension	Injection: 1.25 mg/mL	✔
Fosinopril (Monopril®*)	Heart failure, hypertension	Tablet: 10 mg 20 mg 40 mg	✔
Lisinopril (Prinivil®*, Zestril®*)	Acute myocardial infarction to improve survival, heart failure, hypertension	Tablet: 2.5 mg 5 mg 10 mg 20 mg 30 mg 40 mg	✔
Moexipril (Univasc®*)	Hypertension	Tablet: 7.5 mg 15 mg	✔
Perindopril	Hypertension, stable coronary artery disease to	Tablet:	✔

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Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Aceon®*)	reduce the risk of cardiovascular mortality or nonfatal myocardial infarction	2 mg 4 mg 8 mg	
Quinapril (Accupril®*)	Heart failure, hypertension	Tablet: 5 mg 10 mg 20 mg 40 mg	✔
Ramipril (Altace®*)	Heart failure post myocardial infarction, hypertension, reduce the risk of myocardial infarction, stroke and death from cardiovascular causes	Capsule: 1.25 mg 2.5 mg 5 mg 10 mg Tablet: 1.25 mg 2.5 mg 5 mg 10 mg	✔
Trandolapril (Mavik®*)	Heart failure post-myocardial infarction, hypertension, left ventricular dysfunction post-myocardial infarction	Tablet: 1 mg 2 mg 4 mg	✔

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

Evidence-based Medicine

- Angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective for coronary artery disease and to reduce the risk of cardiovascular mortality, myocardial infarction and stroke.[19-30]
- Clinical Trials have demonstrated the efficacy of ACE inhibitors in reducing mortally associated with congestive heart failure.[31-47]
- ACE inhibitors have demonstrated efficacy for the treatment for hypertension and for the use in diabetic nephropathy.[48-79]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Treatment guidelines for the management of stable angina recommend angiotensin-converting enzyme (ACE) inhibitors in patients with a left ventricular ejection fraction ≤40% and in those with hypertension, diabetes or chronic kidney disease. ACE inhibitors are also recommended in patients at lower risk (mildly reduced or normal left ventricular ejection fraction) in whom cardiovascular risk factors remain well controlled and revascularization has been performed.[80,81]
  - Treatment guidelines for the management of unstable angina/non-ST elevation myocardial infarction recommend the use of ACE inhibitors in the first 24 hours in patients with or without pulmonary congestion or left ventricular ejection fraction of ≤40%. ACE inhibitors are recommended in patients with heart failure, left ventricular dysfunction, diabetes or hypertension. In addition, ACE inhibitors are a reasonable for patients with heart failure and left ventricular ejection fraction >40% and patients without hypertension or diabetes.[82,83] The guidelines are similar for the management of ST-elevation myocardial infarction.[84-87]
  - Treatment guidelines recommend ACE inhibitors in patients who are at risk for the development of heart failure. ACE inhibitors are recommended for the management of heart failure in patients who have cardiac structural abnormalities or remodeling who have not

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developed heart failure symptoms, especially in patients with reduced left ventricular ejection fraction and a history of myocardial infarction.[88-91]
  - Treatment guidelines for hypertension recommend the use of ACE inhibitors as a first line option in all patients as well as in hypertensive patients with certain compelling indications including heart failure, post-myocardial infarction, left ventricular dysfunction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention.[92-96]
  - Treatment guidelines for the management of hypertension in patients with diabetes recommend a regimen including an ACE inhibitor. In patients with known cardiovascular disease, a regimen including an ACE inhibitor should be used to reduce the risk of cardiovascular events. In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension and microalbuminuria, ACE inhibitors have been shown to delay the progression to macroalbuminuria.[97]
- Other Key Facts:
  - Clinical trials have not demonstrated significant differences when ACE inhibitors were compared to angiotensin II receptor blockers.[30,39-42,47,50,52,60,79]

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Therapeutic Class Review
Angiotensin-Converting Enzyme (ACE) Inhibitors
Single Entity Agents

Overview/Summary

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

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

The single entity ACE inhibitors included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. With the exception of Epaned® (enalapril solution), all of the ACE inhibitors are available generically.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Benazepril (Lotensin®*)	Angiotensin-converting enzyme inhibitor	✔
Captopril (Capoten®*)	Angiotensin-converting enzyme inhibitor	✔
Enalapril (Epaned®, Vasotec®*)	Angiotensin-converting enzyme inhibitor	✔
Enalaprilat*	Angiotensin-converting enzyme inhibitor	✔
Fosinopril (Monopril®*)	Angiotensin-converting enzyme inhibitor	✔
Lisinopril (Prinivil®*, Zestril®*)	Angiotensin-converting enzyme inhibitor	✔
Moexipril (Univasc®*)	Angiotensin-converting enzyme inhibitor	✔
Perindopril (Aceon®*)	Angiotensin-converting enzyme inhibitor	✔
Quinapril (Accupril®*)	Angiotensin-converting enzyme inhibitor	✔
Ramipril (Altace®*)	Angiotensin-converting enzyme inhibitor	✔
Trandolapril (Mavik®*)	Angiotensin-converting enzyme inhibitor	✔

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

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Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[5-18]

Indication(s)	Benazepril	Captopril	Enalapril	Enalaprilat	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Cardiovascular Risk Reduction											
In patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes										✔	
Stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction								✔			
Diabetic Nephropathy											
Treatment of diabetic nephropathy in patients with type 1 insulin-dependent diabetes and retinopathy		✔									
Heart Failure											
Congestive heart failure		✔*	✔*								
Heart failure					✔†	✔‡			✔†		
Hypertension											
Hypertension	✔§	✔‖	✔‖		✔§	✔‖	✔§	✔‖	✔§	✔§	✔‖
Left Ventricular Dysfunction											
Decrease the rate of the development of overt heart failure and decrease the incidence of hospitalization for heart failure in clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤35%)			✔								
Myocardial Infarction											
Hemodynamically stable patients within 24 hours of acute myocardial infarction to improve survival						✔					
Improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction ≤40% and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients		✔									
Stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute										✔	

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Indication(s)	Benazepril	Captopril	Enalapril	Enalaprilat	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
myocardial infarction											
Stable patients who have evidence of left ventricular systolic dysfunction or who are symptomatic from congestive heart failure within the first few days after sustaining acute myocardial infarction											✔

*Usually in combination with diuretics and digitalis.
† As adjunctive therapy when added to conventional therapy including diuretics with or without digitalis.
‡ As adjunctive therapy in patients who are not responding adequately to diuretics and digitalis.
§ May be used alone or in combination with thiazide diuretics.
‖ May be used alone or in combination with other antihypertensive agents.

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Pharmacokinetics

Table 3 outlines important pharmacokinetic properties of the single entity angiotensin-converting enzyme (ACE) inhibitors. All of the ACE inhibitors are prodrugs, with the exception of captopril and lisinopril.[5-18] Captopril and moexipril should be taken one hour before meals since food significantly reduces their absorption.

Table 3. Pharmacokinetics[5-18]

Generic Name	Bioavailability (%)	Protein Binding (%)	Elimination (%)	Active Metabolites	Half-Life (hours)
Benazepril	≥37	~96.7*	Bile (11 to 12)*; renal (20)*	Yes, benazeprilat	10 to 11*
Captopril	≥75	~25 to 30	Renal (>95)	None	<2
Enalapril	~60	50 to 60	Feces; renal (60 to 80)	Yes, enalaprilat	11*
Enalaprilat	Not reported	Not reported	Renal (>90)	None	35 to 38
Fosinopril	~36	~ 100*	Feces (50); renal (50)	Yes, fosinoprilat	12*
Lisinopril	~25	None	Renal (100)	None	12
Moexipril	~13	~50*	Feces (53); renal (13)	Yes, moexiprilat	2 to 9*
Perindopril	~75	60 (10 to 20)*	Renal	Yes, perindoprilat	1 (3 to 10)*
Quinapril	≥60	~97	Renal	Yes, quinaprilat	2*
Ramipril	≥50 to 60	73 (56)*	Feces (40); renal (60)	Yes, ramiprilat	9 to18*
Trandolapril	10 (70)*	80	Feces (66); renal (33)	Yes, trandolaprilat	6 (10)*

*Active metabolite.

Clinical Trials

Angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective for coronary artery disease and to reduce the risk of cardiovascular mortality, myocardial infarction and stroke.[19-30] Additionally, in a retrospective analysis, ramipril was associated with significantly lower mortality one year after myocardial infarction compared to captopril, enalapril, fosinopril, lisinopril and quinapril. There were no significant difference between ramipril and perindopril.[27] When compared to angiotensin II receptor blockers (ARBs), no significant differences in blood pressure related risk reductions were noted.[30]

Clinical Trials have demonstrated the efficacy of ACE inhibitors in reducing mortally associated with congestive heart failure.[31-47] No significant differences were noted when ACE and ARBs were compared.[39-42,47]

ACE inhibitors have demonstrat80ed efficacy for the treatment for hypertension.[48-69] Both lisinopril and trandolapril had greater reductions in blood pressure compared to captopril.[56,63] Trandolapril also had greater reduction in blood pressure than enalapril.[61] When compared to ARBs, enalapril had similar reductions in blood pressure compared to telmisartan and eprosartan, but ramipril had lower reductions in blood pressure compared to telmisartan.[50,52,60]

ACE inhibitors have also shown efficacy for the use in diabetic nephropathy.[65-79] In a meta-analysis comparing ACE inhibitors to ARBs, there was no significant difference in all-cause mortality between treatment groups.[79]

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Clinical Trials

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Coronary Artery Disease				
Swedberg et al[19] CONSENSUS II Enalapril 5 to 20 mg/day vs placebo Treatment was started with an intravenous infusion of 1 mg of enalaprilat administered over 3 hours followed by oral enalapril 6 hours after the infusion was stopped.	DB, MC, PC, PG, RCT Patients (mean of 66 years of age) who presented within 24 hours of the onset of acute MI symptoms	N=6,090 180 days	Primary: Mortality rates within six months Secondary: Mortality within one month, cause of death, re-infarction, or worsening heart failure	Primary: Mortality rates according to life-table analysis between the enalapril and placebo groups at 6 months were not significantly different (11.0 vs 10.2%; P=0.26). The RR associated with enalapril treatment and based on the mortality curves was 1.10 (95% CI, 0.93 to 1.29). Secondary: Mortality rates between the enalapril and placebo groups at one month were not significantly different (7.2 vs 6.3%; P=0.26). Death due to progressive heart failure occurred more frequently in patients treated with enalapril than placebo (4.3 vs 3.4%; P=0.06). There were no significant differences in the rate of reinfarction between the enalapril or placebo groups (P=NS). Change in therapy because of heart failure occurred more in the placebo group (P<0.006) but there were no significant differences in hospitalization for heart failure (P=NS). Note: The first CONSENSUS trial excluded patients with a recent myocardial infarction or unstable angina. The study was stopped early after recruiting 6,090 of the intended 9,000 patients since more patients had died on the drug than on placebo (although the difference was not statistically significant).
Pitt et al[20] 4E-Left Ventricular Hypertrophy Study Enalapril 40 mg QD vs	AC, DB, PG, RCT Patients with left ventricular hypertrophy, a history of HTN	N=153 9 months	Primary: Change in left ventricular mass as assessed by MRI Secondary: Reduction in SBP	Primary: Both treatments were associated with a significant reduction in left ventricular mass from baseline (P<0.001). The difference in left ventricular mass reduction from baseline between the two treatments was not significant (P=0.258). While enalapril plus eplerenone therapy demonstrated a significantly greater reduction in left ventricular mass from baseline compared to eplerenone

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
eplerenone 200 mg QD vs enalapril 10 mg plus eplerenone 200 mg If the BP was uncontrolled on study medication at week 8, OL HCTZ 12.5 to 25 mg/day and/or amlodipine 10 mg/day were allowed.	and predominantly in sinus rhythm		and DBP, response rate (DBP <90 mm Hg), change in urine albumin creatinine ratio	therapy (P=0.007); the effect was not statistically different from that observed with enalapril therapy (P=0.107). Secondary: The SBP was reduced significantly more in enalapril plus eplerenone-treated patients compared to eplerenone-treated patients (P=0.048). The other treatment groups exhibited statistically comparable reductions from baseline in mean SBP and DBP (P value not reported). While 70.0% of eplerenone-treated patients responded to therapy, 40.7% of enalapril-treated patients responded (P=0.003). In addition, 79.6% of enalapril plus eplerenone-treated patients responded to therapy compared to 40.7% enalapril-treated patients (P=0.001). Enalapril plus eplerenone therapy was associated with a significant reduction in urine albumin creatinine ratio compared to either eplerenone or enalapril therapy (P<0.05). Adverse events were reported with similar incidence among all treatment groups (P value not reported). Cough was significant in enalapril-treated patients compared to eplerenone-treated patients (P=0.033). Two cases of gynecomastia were reported (one eplerenone- and one enalapril plus eplerenone-treated patients). Four patients (three enalapril- and one enalapril plus eplerenone-treated patients) experienced impotence during the trial. Seven eplerenone-, two enalapril- and three enalapril plus eplerenone-treated patients experienced serious hyperkalemia (≥6.0 mmol/L).
Fox et al[21] EUROPA Perindopril 8 mg QD vs placebo	DB, MC, PC, RCT Men and women ≥18 years of age (mean 60 years) without clinical heart failure or uncontrolled HTN	N=12,218 4.2 years (mean)	Primary: Composite of cardiovascular death, MI, or cardiac arrest Secondary: Composite of total mortality, nonfatal	Primary: Patients treated with perindopril had a significant reduction in the primary outcome compared to patients treated with placebo (8 vs 10%; RRR, 20%; 95% CI, 9 to 29; P=0.0003). The benefit began to appear at one year and gradually increased throughout the trial. Secondary: Compared to placebo, treatment with perindopril was associated with reductions in all secondary end points. However, not all changes were

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	with stable CAD and evidence of CHD (e.g., MI >3 months before screening, percutaneous or surgical coronary revascularization >6 months before screening, 70% narrowing of 1 or more major coronary arteries, history of chest pain)		MI, hospital admission for unstable angina, and cardiac arrest with successful resuscitation; cardiovascular mortality and nonfatal MI; individual components of the secondary outcomes and revascularization, stroke, and admission for heart failure	significant. There was a 14% reduction in total mortality, nonfatal MI, unstable angina, and cardiac arrest (P=0.0009). There was a 22% reduction in nonfatal MI with perindopril (P=0.001). Total mortality was 11% lower with perindopril but this finding was not significant (P=0.1). Hospital admission for heart failure was significantly reduced with perindopril by 39% (P=0.002).
PREAMI Investigators[22] Perindopril 8 mg/day vs placebo	DB, MC, PC, PG, RCT Patients ≥65 years of age with LVEF ≥40% and recent acute MI	N=1,252 12 months	Primary: Composite of death, hospitalization for heart failure or left ventricular remodeling Secondary: Cardiovascular death, hospitalization for reinfarction or angina, revascularization	Primary: The primary end point occurred in 35% of patients taking perindopril and 57% of patients on placebo, with a significant ARR, 0.22 (95% CI, 0.16 to 0.28; P<0.001). A total of 126 patients (28%) and 226 patients (51%) in the perindopril and placebo groups, respectively, experienced remodeling (P<0.001). The mean increase in left ventricular end-diastolic volume was 0.7 mL with perindopril compared to 4.0 mL with placebo (P<0.001). Secondary: Cardiovascular death, hospitalization for subsequent acute MI or angina or revascularization was infrequent and not modified by treatment. Conclusion: Perindopril treatment for one year reduced progressive left ventricular remodeling but was not associated with better clinical outcomes.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
PROGRESS[23] Perindopril (4 mg/day) vs perindopril (4 mg/day) and indapamide (2.5 mg/day or 2.0 mg/day in Japan) vs placebo	DB, MC, PC, RCT Patients with an average age of 64 years with a history of prior stroke or TIA within the previous 5 years	N=6,105 4 years	Primary: Fatal or nonfatal stroke Secondary: Fatal or disabling stroke, total major vascular events comprising the composite of nonfatal stroke, nonfatal MI, or death due to any vascular cause (including unexplained sudden death); total and cause specific deaths; hospital admissions	Primary: Patients receiving active treatment experienced a 28% reduction in nonfatal or fatal stroke (95% CI, 17 to 38; P<0.0001). There were similar reductions in the risk of stroke in hypertensive and nonhypertensive subgroups (32 vs 27%; P<0.01) A trend towards a greater effect of active treatment among patients treated with combination therapy (43% risk reduction) than in those treated with single drug therapy (5% risk reduction) was reported (P value not reported). Secondary: There was a 33% reduction in fatal or disabling strokes in the active treatment group (P value not reported). Active treatment reduced the risk of total major vascular events by 26% (P=0.02). There were no significant differences between active treatment and placebo in total deaths from vascular or nonvascular causes (P value not reported). Among those assigned active treatment, there was a 9% RRR in hospitalization, with a median reduction of 2.5 days in the time spent in the hospital during follow-up (P value not reported). Combination therapy with perindopril plus indapamide reduced BP by 12/5 mm Hg and stroke risk by 43%. Single drug therapy reduced BP by 5/3 mm Hg and produced no discernable reduction in the risk of stroke.
HOPE Investigators[24] Ramipril 10 mg QD vs placebo	DB, RCT, two-by-two factorial trial Men and women ≥55 years of age with history of	N=9,297 5 years (mean)	Primary: Composite of death from cardiovascular causes, MI, or stroke and each outcome	Primary: Fewer patients on ramipril than placebo (14.0 vs 17.8%, respectively) died of cardiovascular causes or had a MI or stroke (RR, 0.78; 95% CI, 0.70 to 0.86; P<0.001). Treatment with ramipril reduced the rates of death from cardiovascular causes (RR, 0.74; P<0.001), MI (RR, 0.80; P<0.001), and stroke (RR, 0.68; P<0.001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Note: the trial also evaluated vitamin E but those results were not included in this review.	CAD, stroke, PVD, or diabetes and at least one other cardiovascular risk factor and who were not known to have a low ejection fraction (<40%) or heart failure		separately Secondary: Death from any cause, revascu-larization, hospitalization for unstable angina or heart failure, and complications related to diabetes, worsening angina, cardiac arrest, heart failure, unstable angina with ECG changes, and the development of diabetes	Secondary: The risk of death from any cause was also significantly reduced by treatment with ramipril (RR, 0.84; P=0.005). Significantly fewer patients treated with ramipril underwent revascularization compared to placebo (RR, 0.85; P=0.002). Fewer hospitalizations for heart failure were reported with ramipril vs placebo but the risk reduction was not statistically significant (RR, 0.88; P=0.25). Fewer complications related to diabetes were reported in patients receiving ramipril (RR, 0.84; P=0.03). Other end points: Significantly fewer patients treated with ramipril than placebo group had the following: worsening angina (RR, 0.89; P=0.004), cardiac arrest (RR, 0.62; P=0.02), heart failure (RR 0.77; P<0.001), and new diagnosis of diabetes (RR, 0.66; P<0.001). There was no difference between treatment groups for unstable angina with ECG changes (RR, 0.97; P=0.76). Note: Patients were excluded if they had heart failure or were known to have a low ejection fraction (<40%).
ONTARGET Investigators[25] Ramipril 10 mg/day vs telmisartan 80 mg/day vs ramipril 10 mg/day and telmisartan 80 mg/day	DB, MC, PC, RCT Men and women (mean age 66.4 years in the ramipril and telmisartan arms and 66.5 years in the combination arm) with coronary,	N=25,620 56 months (median follow-up)	Primary: Death from cardiovascular causes, MI, stroke or hospitalization for heart failure Secondary: Composite of death from cardiovascular causes, MI or	Primary: The primary outcome occurred in 16.5, 16.7 and 16.3% of patients receiving ramipril, telmisartan and combination therapy, respectively (P values not reported). Secondary: The composite of death from cardiovascular causes, MI or stroke occurred in 14.1% of patients in the ramipril group and 13.9% of patients in the telmisartan group (RR, 0.99; 95% CI, 0.91 to 1.07; P=0.001 for noninferiority). Combination therapy was not significantly better than ramipril alone (RR, 0.99; 95% CI, 0.92 to 1.07).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	peripheral, or cerebrovascular disease or diabetes with end-organ damage		stroke; heart failure, worsening or new angina, new diagnosis diabetes mellitus, new atrial fibrillation, renal impairment, revascularization procedures	There were no significant differences in the rates of secondary outcomes, except for renal dysfunction, which occurred in 10.2% of patients receiving ramipril, 10.6% of patients receiving telmisartan and 13.5% of patients receiving combination therapy (P<0.001 vs ramipril; no P value reported vs telmisartan). As compared to the ramipril group, the telmisartan group had lower rates of cough (1.1 vs 4.2%; P<0.001) and angioedema (0.1 vs 0.3%; P=0.01) and a higher rate of hypotensive symptoms (2.6 vs 1.7%; P<0.001); the rate of syncope was the same in the two groups (0.2%). As compared to the ramipril group, combination therapy had an increased risk of hypotensive symptoms (4.8 vs 1.7%; P<0.001), syncope (0.3 vs 0.2%; P=0.03) and renal dysfunction (13.5 vs 10.2%; P<0.001).
PEACE Trial Investigators[26] Trandolapril (target 4 mg/day) vs placebo	DB, PC, RCT Men and women ≥50 years of age with stable CAD and normal or slightly reduced left ventricular function (LVEF >40% with mean 58%)	N=8,290 4.8 years (median)	Primary: Combined rate of nonfatal MI, death from cardiovascular causes, or coronary revascularization procedures Secondary: Combinations of death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, new CHF, stroke, PVD, and	Primary: No significant differences in the primary outcome measures between trandolapril and placebo were reported (21.9 vs 22.5%; HR, 0.96; 95% CI, 0.88 to 1.06; P=0.43). Secondary: No significant differences in secondary outcome measures between trandolapril and placebo were reported (P>0.05). Side effects leading to discontinuation of study medication occurred in 14.4% of patients receiving trandolapril and 6.5% of patients receiving placebo (P<0.001). The rates of cough (39.1 vs 27.5%; P<0.01) and syncope (4.8 vs 3.9%; P=0.04) were higher in patients receiving trandolapril vs placebo. Note: This trial was conducted in low-risk patients with stable CAD and normal or slightly reduced left ventricular function. However, the HOPE trial was conducted in patients with coronary or other vascular disease or with diabetes and another cardiovascular risk factor and the EUROPA trial was conducted in patients with evidence of CHD.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			cardiac arrhythmia	
Pilote et al[27] Captopril (50 mg), enalapril (10 mg), fosinopril (10 mg), lisinopril (10 mg), perindopril (4 mg), quinapril (20 mg), and ramipril (5 mg); (mean values of actual dosages)	Nonrandomized, RETRO, cohort trial (Canada) Patients ≥65 years of age who were hospitalized for acute MI and filled a prescription for an ACE inhibitor within 30 days of discharge and who continued to receive the same drug for at least 1 year	N=7,512 Average of 2.3 years since discharge	Primary: One-year mortality following an acute MI Secondary: Readmissions due to cardiac complications	Primary: Captopril (HR, 1.56; 95% CI, 1.13 to 2.15), enalapril (HR, 1.47; 95% CI, 1.14 to 1.89), fosinopril (HR, 1.71; 95% CI, 1.29 to 2.25), lisinopril (HR, 1.28; 95% CI, 0.98 to 1.67) and quinapril (HR, 1.58; 95% CI, 1.10 to 2.82) were associated with higher mortality than was ramipril. No statistically significant difference was reported between perindopril and ramipril (HR, 0.98; 95% CI, 0.60 to 1.60; no P value reported). Secondary: Enalapril (HR, 1.44; 95% CI, 1.03 to 2.01) and fosinopril (HR, 1.83; 95% CI, 1.27 to 2.62) were associated with higher readmission rates for CHF than ramipril (no P values reported). Readmissions for unstable angina and recurrent MI were similar across all prescription groups.
Nissen et al[28] CAMELOT Amlodipine tablet (5 mg/day) and placebo enalapril capsule vs placebo amlodipine tablet and enalapril (10 mg/day) capsule vs placebo amlodipine tablet and placebo enalapril	DB, MC, PC, RCT Men and women 30 to 79 years of age requiring coronary angiography for evaluation for chest pain or PCI and a diastolic pressure <100 mm Hg, with or without treatment; patients with left main coronary	N=1,991 2 years	Primary: Incidence of adverse cardiovascular events (cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or nonfatal stroke or TIA, and any new	Primary: Adverse cardiovascular events occurred in 23.1% of placebo-treated patients, 16.6% amlodipine-treated patients (HR, 0.69; 95% CI, 0.54 to 0.88; P=0.003) and 20.2% enalapril-treated patients (HR, 0.85; 95% CI, 0.67 to 1.07; P=0.16). The most frequent component of the primary end point, coronary revascularization, was reduced in the amlodipine group from 15.7 to 11.8% (HR, 0.73; 95% CI, 0.54 to 0.98; P=0.03). Hospitalization for angina was reduced in the amlodipine group from 12.8 to 7.7% (HR, 0.58; 95% CI, 0.41 to 0.82; P =0.002). Individual components of the primary end point generally showed fewer events with enalapril treatment vs placebo, but none of the comparisons reached statistical significance. The primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63 to 1.04; P=0.10).

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capsule Doses were doubled (amlodipine 10 mg/day and enalapril 20 mg/day) after 2 weeks if the initial dose was tolerated. Participants were instructed to take only 1 tablet and 1 capsule of study medication each day if they experienced any intolerable adverse effect thought to be related to the study drug while at full dose.	artery obstruction >50%, LVEF <40% or moderate-to-severe CHF were excluded		diagnosis of PVD), nominal change in percent atheroma volume (substudy) Secondary: Incidence of adverse events; all-cause mortality, incidence of revascularization in vessels that had undergone previous stent placement	For components of the primary end point, only the rate of hospitalization for angina showed a statistically significant difference between amlodipine and enalapril (HR, 0.59; 95% CI, 0.42 to 0.84; P=0.003). A trend toward fewer episodes of revascularization in patients undergoing intervention at baseline was observed for amlodipine vs enalapril (HR, 0.66; 95% CI, 0.40 to 1.06; P=0.09). The mean change in percent atheroma volume was 0.5% for amlodipine (P=0.12 vs placebo), 0.8% for enalapril (P=0.32 vs placebo) and 1.3% for placebo. In patients with SBP greater than the mean, the amlodipine group showed a significantly slower progression (0.2%) compared to placebo (2.3%; P=0.02). Compared to baseline, intravascular ultrasound showed progression in patients receiving placebo (P<0.001), a trend toward progression with enalapril (P=0.08) and no progression in patients receiving amlodipine (P=0.31). For the amlodipine group, correlation between BP reduction and progression was r=0.19 (P=0.07). Secondary: Discontinuation from the study for treatment-emergent adverse events was low, averaging 0.4% and not statistically significant between the three treatment groups (P value not reported). The only statistically significant difference in secondary end points was that amlodipine demonstrated a significant reduction in revascularization after previous stent placement compared to placebo (4.1 vs 7.9%; HR, 0.49; 95% CI, 0.31 to 0.78; P=0.002). The rate of revascularization was lower than enalapril (6.2%) but not statistically significant (HR, 0.66; 95% CI, 0.40 to 1.06; P=0.09).
Dalhof et al[29] ASCOT-BPLA Amlodipine 5 to 10 mg/day adding perindopril 4 to 8 mg/day as needed	MC, OL, PRO, RCT Patients 40 to 79 years of age with HTN and at least	N=19,257 5.5 years	Primary: Nonfatal MI (including silent MI) and fatal CHD Secondary:	Primary: No statistically significant difference in nonfatal MI and fatal CHD was reported between the amlodipine plus perindopril group compared to the atenolol plus bendroflumethiazide groups (HR, 0.90; 95% CI, 0.79 to 1.02; P=0.1052). Secondary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atenolol 50 to 100 mg/day adding bendroflumethiazide 1.25 to 2.5 mg/day and potassium as needed If BP was still not achieved, a third drug, an α-blocker (doxazosin 4 to 8 mg/day), was added to the regimen.	3 other cardiovascular risk factors (left ventricular hypertrophy, other specified abnormalities on ECG, type 2 diabetes, PAD, history of stroke or TIA, male, ≥55 years of age, microalbuminuria or proteinuria, smoking, total cholesterol to HDL-C ratio ≥6, or family history of CHD)		All-cause mortality, total stroke, primary end points minus silent MI, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, nonfatal and fatal heart failure, effects on primary end point and on total cardiovascular events and procedures among prespecified subgroups, silent MI, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias, development of diabetes, development of renal impairment	Significantly greater reductions in the following secondary end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: all- cause mortality (P=0.0247), total stroke (P=0.0003), primary end points minus silent MI (P=0.0458), all coronary events (P=0.0070), total cardiovascular events and procedures (P<0.0001), and cardiovascular mortality (P=0.0010). There were no significant differences in nonfatal and fatal heart failure between the two treatment groups (P=0.1257). The study was terminated early due to higher mortality and worse outcomes on several secondary end points observed in the atenolol study group. Significantly greater reductions in the following end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: unstable angina (P=0.0115), PAD (P=0.0001), development of diabetes (P<0.0001), and development of renal impairment (P=0.0187). There were no significant differences in the incidence of silent MI (P=0.3089), chronic stable angina (P =0.8323) or life-threatening arrhythmias (P=0.8009) between the two treatment groups. There was no significant difference in the percent of patients who stopped therapy because of an adverse event between the two treatment groups (overall 25%; no P values reported). There was, however, a significant difference in favor of amlodipine plus perindopril in the proportion of patients who stopped trial therapy because of a serious adverse events (2 vs 3%; P<0.0001).
Blood Pressure Lowering Treatment Trialists' Collaboration[30] ACE inhibitors (17 trials)	MA of RCT published by the end of 2004 Patients with high BP, diabetes,	N=146,838 (26 trials) Duration varied	Primary: Nonfatal MI or death from CHD, including sudden death; heart failure causing death or	Primary: From a total of 146,838 individuals with high BP or an elevated risk of cardiovascular disease, major cardiovascular events were documented in 22,666 patients during follow-up. The analyses showed comparable BP-dependent reductions in risk with ACE inhibitors and ARBs (P≥0.3 for all three outcomes).

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vs ARBs (9 trials)	history or CHD or cerebrovascular disease		requiring hospitalization; nonfatal stroke or death from cerebrovascular disease Secondary: Not reported	ACE inhibitors produced a BP-independent reduction in the relative risk of CHD of approximately 9% (95% CI, 3 to 14). No similar effect was detected for ARBs, and there was some evidence of a difference between ACE inhibitors and ARBs in this regard (P=0.002). For both stroke and heart failure, there was no evidence of any BP-independent effects of either ACE inhibitors or ARBs. Secondary: Not reported The authors concluded that there are similar BP-dependent effects of ACE inhibitors and ARBs for the risks of stroke, CHD and heart failure. They also stated that for ACE inhibitors but not ARBs there is evidence of BP-independent effects on the risk of major coronary disease events.
Heart Failure Angiotensin-converting Enzyme Inhibitor vs Placebo or Another Angiotensin-converting Enzyme Inhibitor				
Pfeffer et al[31] SAVE Captopril up to 50 mg TID vs placebo	DB, MC, PC, RCT Patients ≥21 and <80 years of age who had an acute MI within 3 to 16 days and left ventricular dysfunction with an ejection fraction ≤40% but without overt heart failure or symptoms of myocardial ischemia	N=2,231 42 months (average)	Primary: Mortality from all causes, mortality from cardiovascular causes, mortality combined with a decrease in ejection fraction of at least 9 units in surviving patients, cardiovascular morbidity (severe CHF or recurrence of a fatal or nonfatal MI), combination of cardiovascular	Primary: Mortality from all causes was significantly reduced in the captopril group (20%) vs placebo group (25%) for a 19% reduction in the risk of mortality from all causes (95% CI, 3 to 25; P=0.019). The incidence of fatal cardiovascular events was consistently reduced in the captopril group with a 21% reduced risk of mortality from cardiovascular causes (P=0.014). The incidence of nonfatal major cardiovascular events was consistently reduced in the captopril group with a 25% reduced risk of recurrent MI (P=0.015), 37% reduced risk for the development of severe heart failure (P<0.001), and 22% reduced risk of CHF requiring hospitalization (P=0.019). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			mortality and morbidity Secondary: Not reported	
CONSENSUS Trial Study Group[32] Enalapril 2.5 to 40 mg per day vs placebo	DB, MC, PC, PG, RCT Patients with severe CHF (NYHA class IV symptoms), patients with recent MI and unstable angina were excluded	N=253 188 days (average)	Primary: Six-month mortality and the cause of death Secondary: 12-month mortality and overall mortality	Primary: Mortality at six months was 26 and 44% for patients in the enalapril and placebo groups, respectively, for an overall reduction of 40% for enalapril (P=0.002). Secondary: At 12 months, enalapril reduced mortality by 31% compared to placebo (P=0.001). By the end of the study, there had been 50 deaths in the enalapril group and 68 deaths in the placebo group for a reduction of 27% (P=0.003). The entire reduction in total mortality was found to be among patients with progressive heart failure (a reduction of 50%), whereas no difference was seen in the incidence of sudden cardiac death. Note: The study was stopped early due to clear benefit with enalapril. On the date of termination, 253 of the planned 400 patients were enrolled.
SOLVD Investigators[33] SOLVD Treatment Trial Enalapril 2.5 to 20 mg/day vs placebo	DB, MC, PC, RCT Patients with CHF (90% were in NYHA class II and III) and LVEF ≤35% receiving conventional therapy	N=2,569 41.4 months (average)	Primary: Mortality, rate of hospitalization for heart failure Secondary: Not reported	Primary: Death was reported in 35.2 and 39.7% of patients receiving enalapril and placebo, respectively (risk reduction, 16%; 95% CI, 5 to 26; P=0.0036). Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive heart failure (risk reduction, 22%; 95% CI, 6 to 35; no P value reported). There was little apparent effect of treatment on deaths classified as due to arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening heart failure (risk reduction, 26%; 95% CI, 18 to 34; P<0.0001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
SOLVD Investigators[34] SOLVD Prevention Trial Enalapril 2.5 to 20 mg /day vs placebo	DB, MC, PC, RCT Patients between 21 to 80 years of age with heart disease and an ejection fraction of ≤35% who were not receiving diuretics, digoxin or vasodilators for the treatment of heart failure	N=4,228 37.4 months (average)	Primary: All-cause mortality, incidence of heart failure, rate of hospitalization for heart failure Secondary: Not reported	Primary: Enalapril resulted in an 8% reduction in risk for all-cause mortality (P=0.30). The difference was entirely due to a reduction in deaths due to cardiovascular causes, primarily progressive heart failure (risk reduction, 12%; P=0.12). In the placebo group, 30.2% of patients developed heart failure compared to 20.7% for enalapril (risk reduction, 37%; P<0.001). Rates of first hospitalization and multiple hospitalizations for CHF were higher with placebo (12.9 and 4.8%) than enalapril (8.7 and 2.7%; both P<0.001). The total number of deaths and cases of heart failure were lower in the enalapril group than in the placebo group (risk reduction, 29%; P<0.001). In addition, fewer patients given enalapril died or were hospitalized for heart failure (risk reduction, 20%; P<0.001). Secondary: Not reported
Tu et al[35] Comparison between enalapril (comparator drug) and lisinopril, ramipril and other ACE inhibitors (benazepril, captopril, cilazapril*, fosinopril, perindopril, quinapril and trandolapril)	RETRO, cohort study Patients >65 years of age with newly diagnosed CHF initiated on ACE inhibitors who survived ≥30 days after hospital discharge	N=6,753 ≤2 years	Primary: Combined end point of readmission for CHF as a primary diagnosis or mortality Secondary: CHF readmission alone and mortality alone	Primary: Relative to enalapril users, there were no significant differences in combined end point of readmission for CHF or mortality with lisinopril (AHR, 1.08; 95% CI, 0.94 to 1.23), ramipril (AHR, 1.06; 95% CI, 0.92 to 1.24) or other ACE inhibitors (AHR, 1.02; 95% CI, 0.90 to 1.17). Secondary: There were no significant differences among groups in readmission for CHF: enalapril 13% (AHR, 1), lisinopril 15% (AHR, 1.11; 95% CI, 0.92 to 1.32), ramipril 15% (AHR, 1.19; 95% CI, 0.99 to 1.45), and other ACE inhibitors 15% (AHR, 1.13; 95% CI, 0.96 to 1.34). There were no significant differences among groups in mortality: enalapril 12% (AHR, 1), lisinopril 13% (AHR, 1.09; 95% CI, 0.90 to 1.31), ramipril 12% (AHR, 0.97; 95% CI, 0.78 to 1.20), and other ACE inhibitors 11% (AHR, 0.94; 95% CI,

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.78 to 1.13).
Packer et al[36] ATLAS Lisinopril low dose (target 2.5 to 5 mg/day) vs lisinopril high dose (target 32.5 to 35 mg/day)	DB, RCT Patients with NYHA class II, III, or IV symptoms of heart failure associated with a LVEF ≤30% despite treatment with diuretics for ≥2 months	N=3,164 39 to 58 months	Primary: All-cause mortality Secondary: cardiovascular mortality, hospitalizations (for any reason and for cardiovascular reasons), combinations of the primary and secondary end points	Primary: High-dose lisinopril was associated with a nonsignificant 8% lower risk of all-cause mortality compared to low-dose lisinopril (P=0.128). Secondary: Cardiovascular mortality was reported in 40.2 and 37.2% of patients receiving low-dose and high-dose lisinopril, respectively (P=0.073). High-dose lisinopril resulted in a 12% lower risk of death or hospitalizations for any reason (P=0.002), a 9% lower risk of cardiovascular mortality and hospitalization for cardiovascular reason (P=0.027) and 24% fewer hospitalizations for heart failure (P=0.002). Dizziness and renal insufficiency were observed more frequently in the high-dose group, but the two groups were similar in the number of patients requiring discontinuation of the study medication.
AIRE Study Investigators[37] Ramipril 2.5 to 5 mg BID vs placebo Treatment was begun on day 3 to 10 after acute MI.	DB, MC, PC, RCT Men and women at least 18 years of age with acute MI and clinical evidence of heart failure, patients with severe heart failure (e.g., NYHA grade IV) were excluded	N=2,006 15 months (average)	Primary: All-cause mortality Secondary: First event in an individual patient (death, progression to severe/resistant heart failure, re-infarction, or stroke)	Primary: On the intention-to-treat analysis, all-cause mortality was significantly lower for patients randomized to receive ramipril (17%) than placebo (23%). The observed risk reduction was 27% (95% CI, 11 to 40; P=0.002). Secondary: Analysis of prespecified secondary outcomes revealed a 19% risk reduction in the ramipril group compared to placebo (95% CI, 5 to 31; P=0.008).
Kober et al[38] TRACE Trandolapril 1 to 4 mg QD	DB, MC, PC, RCT Men and women >18 years of age	N=1,749 24 to 50 months	Primary: Death from any cause Secondary:	Primary: During the study, 34.7% of patients in the trandolapril group died compared to 42.3% in the placebo group (P=0.001). The relative risk of death in the trandolapril group was 0.78 compared to placebo (95% CI, 0.67 to 0.91).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Medication was started between day 3 and 7 after the MI.	who were hospitalized with a recent MI and an LVEF ≤35%		Death from a cardiovascular cause, sudden death, progression to severe heart failure (defined as the first of the following events: hospital admission for heart failure, death due to progressive heart failure, or heart failure necessitating the administration of open-label ACE inhibition), recurrent infarction, change in the wall-motion index	Secondary: Trandolapril reduced the risk of death from cardiovascular causes (RR, 0.75; 95% CI, 0.63 to 0.89; P=0.001) and sudden death (RR, 0.76; 95% CI, 0.59 to 0.98; P=0.03). Progression to severe heart failure was less frequent in the trandolapril group (RR, 0.71; 95% CI, 0.56 to 0.89; P=0.003). The risk of recurrent fatal or nonfatal MI was not significantly reduced (RR, 0.86; 95% CI, 0.66 to 1.13; P=0.29). After three months, the mean change from the base-line index was 0.09 in the trandolapril group and 0.06 in the placebo group (P=0.03) but this statistically significant difference was absent at six and 12 months.
Heart Failure (Angiotensin-converting Enzyme Inhibitor vs Agents From Other Therapeutic Classes)				
Pitt et al[39] ELITE Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥65 years of age with symptomatic heart failure (NYHA class II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=722 1 year	Primary: Change in renal function Secondary: Composite of death and/or hospital admission for heart failure, all-cause mortality, admission for heart failure, NYHA class, admission	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups). Secondary: Death and/or hospital admission for heart failure was recorded in 9.4% of patients receiving losartan and 13.2% for patients receiving captopril (risk reduction, 32%; 95% CI, –4 to 55; P=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8 vs 8.7%; risk reduction, 46%; 95% CI, 5 to 69; P=0.035). Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline. Admission to hospital for

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			for MI or unstable angina	any reason was less frequent with losartan than with captopril treatment (22.2 vs 29.7%; P=0.014). More patients discontinued therapy due to adverse events with captopril (20.8) than losartan (12.2%; P=0.002).
Pitt et al[40] ELITE II Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥60 years of age with symptomatic heart failure (NYHA II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=3,152 555 days (mean follow-up)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between losartan (17.7%) and captopril (15.9%; HR, 1.13; 95% CI, 0.95 to 1.35; P=0.16). Secondary: Sudden death or resuscitated cardiac arrest was observed in 9.0% of patients receiving losartan and 7.3% of patients receiving captopril (HR, 1.25; 95% CI; 0.98 to 1.60; P=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse events (9.7 vs 14.7%; P<0.001), including cough (0.3 vs 2.7%). Note: ELITE II trial was a larger follow-up trial to the ELITE I trial to confirm the secondary end point from the ELITE I trial which reported a greater reduction in all-cause mortality with losartan compared to captopril.
Dickstein et al[41] OPTIMAAL Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥50 years of age (mean age 67.4 years) with an acute MI and signs or symptoms of heart failure during the acute phase or a new Q-wave anterior	N=5,477 2.7 years (mean)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between patients receiving losartan and captopril (18 vs 16%, respectively; RR, 1.13; 95% CI, 0.99 to 1.28; P=0.07). Secondary: No significant difference in sudden cardiac death or resuscitated cardiac arrest was reported between patients receiving losartan and captopril (9 vs 7%; RR, 1.19; 95% CI, 0.98 to 1.43; P=0.07). Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (17 vs 23%; P<0.0001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	infarction or reinfarction			
Pfeffer et al[42] VALIANT Captopril 50 mg TID vs valsartan 160 mg BID vs combination valsartan 80 mg BID and captopril 50 mg TID	DB, MC, RCT Men and women ≥18 years of age with an acute MI that was complicated by clinical or radiologic signs of heart failure and/or evidence of left ventricular systolic dysfunction	N=14,703 24.7 months	Primary: All-cause mortality Secondary: Death from cardiovascular causes, recurrent MI, hospitalization for heart failure	Primary: No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (P=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (P=0.73). Secondary: The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (P=0.20). The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (P=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash, and taste disturbance were more common in the captopril group.
McKelvie et al[43] RESOLVD Pilot Study Enalapril 10 mg BID vs candesartan 4 to 16 mg QD vs combination candesartan 4 to 8 mg QD and enalapril	DB, PG, MC, RCT Patients with CHF (NYHA classes II to IV), a 6 minute walk distance of 500 meters or less, and an ejection fraction <40%	N=768 43 weeks	Primary: Change in six-minute walk distance Secondary: Change in NYHA functional class, quality of life, ejection fraction, ventricular volumes, neurohormone	Primary: There were no significant differences among the groups with regards to the six-minute walk distance over the 43-week study period (P value not reported). Secondary: There were no significant differences among the groups with regards to the NYHA functional class or quality of life at 18 or 43 weeks (P values not reported). Ejection fraction increased more with candesartan plus enalapril than monotherapy with either agent; however, the difference was not statistically significant (P=NS). End-diastolic volumes (P<0.01) and end-systolic volumes (P<0.05) increased less with combination therapy than with monotherapy with

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10 mg BID			levels, safety	either agent. Aldosterone decreased with combination therapy at 17 but not 43 weeks compared to candesartan or enalapril (P<0.05). Brain natriuretic peptide decreased with combination therapy compared to candesartan and enalapril alone (P<0.01). BP decreased with combination therapy compared to candesartan or enalapril alone (P<0.05). Compared to enalapril, potassium decreased with candesartan use (P<0.05) and increased with candesartan plus enalapril (P<0.05). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups. There were no significant differences in creatinine, mortality, or hospitalizations for CHF or any cause among the three groups.
Dobre et al[44] CIBIS III Enalapril 2.5 mg BID titrated up to target dose of 10 mg QD vs bisoprolol 1.25 mg QD titrated up to target dose of 10 mg QD	MC, OL, PRO, RCT Patients ≥ 65 years of age with mild to moderate heart failure, LVEF ≤35%	N=1,010 6 months	Primary: Combined outcome of all cause mortality or all cause hospitalization Secondary: Individual endpoints of combined outcomes, and cause of death and hospitalization	Primary: There was no significant difference in the proportion of patients that met the primary endpoint of all cause mortality or hospitalization between the bisoprolol group (21.6%) and enalapril group (21.4%; HR, 1.02; 95% CI, 0.78 to 1.33; P=0.9). Secondary: The individual endpoint of death was not significantly different between the bisoprolol group and enalapril group (4.6 vs 6.3%; HR, 0.72; 95% CI, 0.42 to 1.24; P=0.24). In addition, the individual endpoint of hospitalization was not significantly different between the bisoprolol group and enalapril group (19.6 vs 18.2%; HR, 1.08; 95% CI, 0.81 to 1.43; P=0.59). There was no significant difference between the groups with respect to cause of death (sudden, non-sudden, unclassifiable; P=0.11, P=0.88, P=0.91, respectively). There was no significant difference in cardiovascular hospitalizations between the groups (P=0.32). There were more patients with worsening heart failure

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				requiring hospitalization or worsening heart failure while in hospital in the bisoprolol group compared to enalapril (8.9 vs 5.3%; HR, 1.67; 95% CI, 1.04 to 2.70; P=0.03). There was no significant difference in discontinuation of treatment due to adverse effects. The most common adverse events in the bisoprolol group were worsening of heart failure, hypotension, bradycardia, respiratory disorders. The most common adverse events in the enalapril group were cough, hypotension, allergic reactions and gastrointestinal disorders.
Willenheimer et al[45] CIBIS III Bisoprolol 1.25 to 10 mg QD vs enalapril 2.5 to 10 mg BID After 26 weeks, all patients received combination therapy with both medications. Patients who were randomized to bisoprolol, received combination therapy with enalapril at 26 weeks (bisoprolol-first group). Patients who were randomized to enalapril, received combination	BE, MC, OL, PG, RCT Patients ≥65 years of age with stable, mild to moderate CHF (NYHA Class II to III HF), LVEF ≤35% ≥3 months prior to randomization, not receiving an ACE inhibitor, β-blocker or ARB and no clinically relevant fluid retention of diuretic adjustment within the 7 days prior to randomization	N=1,010 1.22±0.42 years	Primary: Combined all-cause mortality or hospitalization Secondary: Composite of the primary endpoint at the end of the monotherapy phase, the individual components of the primary end point, cardiovascular death and cardiovascular hospitalization, permanent treatment cessation or the need for early introduction of the second drug as indicators of drug tolerability	Primary: There were 178 patients (35.2%) with a primary end point of combined all-cause mortality or all-cause hospitalization receiving bisoprolol-first group, compared to 186 (36.8%) patients receiving enalapril-first group (absolute difference, -1.6%; 95% CI, -7.6 to 4.4; HR, 0.94; 95% CI, 0.77 to 1.16; noninferiority for bisoprolol-first vs enalapril-first treatment; P=0.019). Secondary: The combined endpoint at the end of the monotherapy phase occurred in 109 patients receiving bisoprolol-first group compared to 108 patients receiving enalapril-first group (HR, 1.02; 95% CI, 0.78 to 1.33; between-group difference; P=0.90); 23 vs 32 patients died, respectively (HR, 0.72; 95% CI, 0.42 to 1.24; between-group difference; P=0.24) and 99 vs 92 patients had been hospitalized, respectively (HR, 1.08; 95% CI, 0.81 to 1.43; between-group difference; P=0.59). There were 65 deaths with bisoprolol-first, as compared to 73 with enalapril-first (HR, 0.88; 95% CI, 0.63 to 1.22; between-group difference; P=0.44). With bisoprolol-first, 151 patients were hospitalized, compared to 157 with enalapril-first (HR, 0.95; 95% CI, 0.76 to 1.19; between-group difference; P=0.66). There was not a significant difference in cardiovascular death rate observed between bisoprolol-first and enalapril-first (55 vs 56; HR, 0.97; 95% CI, 0.67 to 1.40; between-group difference; P=0.86).

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therapy with bisoprolol at 26 weeks (enalapril-first group).				During the monotherapy phase, 35 (6.9%) patients receiving bisoprolol-first permanently discontinued therapy, compared to 49 patients (9.7%) with enalapril-first. During the combined-therapy phase, 19 patients (4.2%) receiving bisoprolol-first permanently discontinued bisoprolol therapy and 47 patients (10.4%) discontinued enalapril therapy. With enalapril-first, 24 patients (5.5%) permanently discontinued bisoprolol and 16 patients (3.7%) discontinued enalapril (P values were not reported). There was not a significant difference observed in the early introduction of the second drug between bisoprolol-first (39 [7.7%] patients) and enalapril-first (37 [7.3%] patients; P=0.81).
Cohn et al[46] V-HEFT II Enalapril 20 mg daily vs hydralazine 300 mg plus isosorbide dinitrate 160 mg daily	AC, DB, MC, RCT Men between 18 and 75 years of age with chronic heart failure receiving digoxin and diuretic therapy	N=804 2 years	Primary: Mortality Secondary: Peak oxygen consumption during exercise, LVEF	Primary: Mortality after two years was significantly lower in the group treated with enalapril (18%) than hydralazine plus isosorbide dinitrate (25%; P=0.016), and overall mortality tended to be lower (P=0.08). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (NYHA class I or II). Secondary: Peak oxygen consumption during exercise was increased only by hydralazine plus isosorbide dinitrate (P<0.05). While LVEF increased with both regimens during the two years after randomization, LVEF increased more (P<0.05) during the first 13 weeks in the hydralazine plus isosorbide dinitrate group.
Lee et al[47] ARBs vs placebo (+/-ACE inhibitor)	MA Patients with chronic heart failure and high-risk acute MI	N=38,080 Duration varied	Primary: All-cause mortality and heart failure hospitalizations Secondary: Not reported	Primary: ARBs were associated with reduced all-cause mortality (OR, 0.83) and heart failure hospitalizations (OR, 0.64) vs placebo. There was no difference in all-cause mortality (OR, 1.06) and heart failure hospitalization (OR, 0.95) between ARBs and ACE inhibitors.

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vs ACE inhibitor monotherapy				When ARBs were combined with ACE inhibitors, all-cause mortality was not reduced (OR, 0.97) but heart failure hospitalizations were reduced (OR, 0.77) compared to treatment with ACE inhibitors alone. Two RCT comparing ARBs with ACE inhibitors in patients with high-risk acute MI did not reveal differences in all-cause mortality or heart failure hospitalization. Secondary: Not reported
Hypertension				
Julien et al[48] Captopril 150 to 300 mg/day vs minoxidil 7.5 to 30 mg/day	DB, PG, RCT Male patients with left ventricular hypertrophy and essential HTN with DBP >95 mm Hg who were taking metoprolol 200 mg/day and furosemide 80 mg/day	N=34 6 months	Primary: Change in BP and left ventricular hypertrophy Secondary: Not reported	Primary: BP decreased significantly with both treatments; captopril (163/102 to 135/89 mm Hg) and minoxidil (160/99 to 137/87 mm Hg) (P<0.001 for both). ECG criteria for left ventricular hypertrophy improved with captopril with only a decrease in intraventricular septum, posterior wall and left ventricular mass (17.4 to 15.9 mm; P<0.05, 14.5 to 13.4 mm; P<0.05 and 236 to 198 g/m^2; P<0.001, respectively). No changes on ECG criteria were observed with minoxidil. Secondary: Not reported
Williams et al[49] Enalapril 10 mg vs eplerenone 50 mg QD Both medications were titrated to 200 (eplerenone)	AC, DB, MC, PG, RCT Patients ≥18 years of age with stage 1 to 2 HTN (seated DBP ≥90 but <110 mm Hg, with a seated SBP <190 mm Hg)	N=499 12 months	Primary: Change in seated trough DBP at six months Secondary: Change in seated trough SBP at six months, reduction in SBP and DBP at 12 months,	Primary: At six months, both treatments exhibited comparable reductions in DBP from baseline (P=0.91). Secondary: At six months, both treatments exhibited comparable reductions in SBP from baseline (P=0.20). At 12 months, both treatments exhibited comparable reductions in SBP and DBP from baseline (P=0.25 and P=0.33).

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or 40 (enalapril) mg/day if needed for optimal BP control (DBP <90 mm Hg).			reduction in urine albumin creatinine ratio, adverse events	Eplerenone-treated patients exhibited a significant reduction from baseline in urine albumin creatinine ratio compared to enalapril-treated patients (61.5 vs 25.7%; P=0.01). There were no significant differences in overall treatment-emergent adverse events between the two treatments (P value not reported). There were no sex hormone related adverse events in eplerenone-treated patients. There were no clinically significant differences between the two treatments in any of the laboratory tests assessed. There were two eplerenone- and enalapril-treated patients that experienced hyperkalemia of ≥5.5 mmol/L.
Ruilope et al[50] Enalapril 5 mg QD (titration to 10 mg followed by 20 mg was allowed every 3 weeks vs eprosartan 600 mg QD (titration to 800 mg QD was allowed after 3 weeks)	DB, MC, PG, RCT Patients greater than 65 years of age with essential HTN, either newly diagnosed or for whom a change in existing antihypertensive medication is indicated due to poor control	N=334 12 weeks	Primary: Mean change from baseline in sitting SBP Secondary: Normalization rate for sitting SBP and DBP, response rate for sitting SBP and DBP, mean change from baseline in DBP	Primary: No significant difference between groups in change from baseline in sitting SBP was observed (P=0.76). Secondary: No significant difference between groups in change from baseline in sitting DBP was observed (P=0.84). BP response rates for SBP and DBP were significantly greater for eprosartan at week 3 ($P \leq 0.033$) but the significant difference had disappeared by endpoint ($P \geq 0.49$). Normalization rates for SBP were low in both groups (P value not reported). Normalization rates for DBP were higher in both groups than SBP normalization rates (P value not reported).
Estacio et al[51] ABCD Enalapril 5 to 40 mg/day vs nisoldipine 10 to 60 mg/day	DB, PRO, RCT Patients between 40 and 74 years of age with NIDDM, baseline DBP ≥90 mm Hg and receiving no antihypertensive	N=470 67 months	Primary: Effect of intensive (target DBP of 75 mm Hg) or moderate (target DBP between 80 and 89 mm Hg) BP control on the incidence and	Primary: Analysis of the 470 patients in the trial who had HTN (DBP ≥90 mm Hg) showed similar control of BP, blood glucose and lipid concentrations between the two study medications throughout the five years of follow-up. Secondary: Nisoldipine was associated with a higher incidence of fatal and nonfatal MI than enalapril (RR, 7.0; 95% CI, 2.3 to 21.4; P value not reported).

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	medications at the time of randomization		progression of complications of diabetes; compare enalapril to nisoldipine as a first-line antihypertensive agent Secondary: Incidence of MI	
Karlberg et al[52] (TEES) Enalapril 5 to 20 mg QD vs telmisartan 20 to 80 mg QD HCTZ 12.5 or 25 mg QD could be added to either group as needed to reach DBP goal (≤90 mm Hg).	DB, DD, MC, PG, RCT Patients ≥65 years of age with mild- to moderate HTN	N=278 26 weeks	Primary: Change from baseline in supine SBP and DBP Secondary: Proportion of responders, safety	Primary: Both treatments had similar rates of HCTZ use. Both treatments showed comparable decreases in BP. Mean changes in DBP were –12.8 mm Hg for telmisartan and –11.4 mm Hg for enalapril (P=0.074). Mean changes in SBP were –22.1 mm Hg for telmisartan and –20.1 mm Hg for enalapril (P=0.350). Secondary: Overall, 63 and 62% of patients responded to telmisartan and enalapril, respectively, with a DBP of <90 mm Hg. Both regimens provided effective BP lowering over the 24-hour dosing interval, as determined by ambulatory BP monitoring. Both regimens were well tolerated; however, the enalapril group had a higher incidence of cough than the telmisartan group (15.8 vs 6.5%; P value reported).
Wing et al[53] ANBP Enalapril and HCTZ were recommended as initial therapy; however, the choice of the specific agent	MC, OL, PRO, RCT Patients 65 to 84 years of age with average SBP while sitting of at	N=6,083 4.1 years (median)	Primary: All cardiovascular events or death from any cause (both initial and subsequent fatal and nonfatal	Primary: By the end of the study, BP had decreased to a similar extent in both groups (a decrease of 26/12 mm Hg). There were 695 cardiovascular events or deaths from any cause in the ACE inhibitor group (56.1 per 1,000 patient-years; HR, 0.89; 95% CI, 0.79 to 1.00; P=0.05) compared to 736 in the diuretic group (59.8 per 1,000 patient-years).

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and dose was made by the family practitioner.	least 160 mm Hg or an average DBP of at least 90 mm Hg (if the SBP was at least 140 mm Hg)		cardiovascular events) Secondary: Not reported	The beneficial effects of ACE inhibitor treatment were more evident in male subjects (HR, 0.83; 95% CI, 0.71 to 0.97; P=0.02). The rates of nonfatal cardiovascular events and MI decreased with ACE inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE inhibitor group). Secondary: Not reported
ALLHAT[54] Lisinopril 10 to 40 mg/day vs amlodipine 2.5 to 10 mg/day vs chlorthalidone 12.5 to 25 mg/day Doses were titrated to achieve a goal BP of <140/90 mm Hg.	DB, MC, RCT Patients ≥55 years of age with HTN and at least 1 additional CHD risk factor	N=33,357 4.9 years (mean follow-up)	Primary: Composite of fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease, cancer, ESRD	Primary: There was no significant difference in the primary outcome between amlodipine- and chlorthalidone-treated patients, or between lisinopril- and chlorthalidone-treated patients (RR, 0.98; 95% CI, 0.90 to 1.07; P=0.65 and RR, 0.99; 95% CI, 0.91 to 1.08; P=0.81). Secondary: In a comparison of lisinopril- and chlorthalidone-treated patients, the secondary endpoints of all-cause mortality, combined CHD, peripheral arterial disease, cancer or end-stage renal disease did not significantly differ. However, there were higher rates of stroke (RR, 1.15; 95% CI, 1.02 to 1.30; P=0.02), combined cardiovascular disease (RR, 1.10; 95% CI, 1.05 to 1.16; P<0.001), heart failure (RR, 1.19; 95% CI, 1.07 to 1.31; P<0.001), angina (hospitalized or treated [RR, 1.11; 95% CI, 1.03 to 1.20; P=0.01]) and coronary revascularizations (RR, 1.10; 95% CI, 1.00 to 1.21; P=0.05) observed in lisinopril-treated patients compared to chlorthalidone-treated patients. The secondary endpoints did not differ between amlodipine- and chlorthalidone-treated patients for all-cause mortality, combined CHD, stroke, combined cardiovascular disease, angina, coronary revascularization, peripheral arterial disease, cancer or end-stage renal disease. However, heart failure and hospitalized/fatal heart failure, components of combined cardiovascular disease, occurred at higher rates in amlodipine-treated patients compared to chlorthalidone-treated patients (RR, 1.38; 95% CI, 1.25 to 1.52;

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				P<0.001 and RR, 1.35; 95% CI, 1.21 to 1.50; P<0.001, respectively).
Whelton et al[55] Lisinopril 10 to 40 mg QD vs captopril 25 to 100 mg BID Doses were titrated until patients responded to treatment (defined by a decrease in office diastolic pressure to <90 mm Hg or at least a 10 mm Hg decrease from baseline).	DB, MC, PG, RCT Patients with mild-to-moderate essential HTN	N=70 Up to 8 weeks	Primary: Reduction in BP in both ambulatory and office settings Secondary: Not reported	Primary: Lisinopril-treated patients showed significantly greater reductions in SBP and DBP measured by 24-hour ambulatory BP monitoring compared to captopril-treated patients (P=0.023 and P=0.007, respectively). Greater reductions (P<0.05) were also noted in patients receiving lisinopril at hours 10 to 12, suggesting two BP troughs for those receiving captopril. The difference in mean reductions between treatment groups from baseline to the final visit approached statistical significance for office SBP (P=0.06) and DBP (P=0.09) in favor of patients receiving lisinopril. Both drugs were well tolerated, and no patients withdrew from either treatment group. Secondary: Not reported
Rosei et al[56] Lisinopril 20 mg QD vs nebivolol 5 mg QD All patients entered a 4 week antihypertensive drug washout period.	DB, MC, PG, RCT Patients 24 to 65 years of age with mild to moderate uncomplicated essential HTN that was newly diagnosed, or previous antihypertensive therapy was withdrawn at >1 month before active treatment, and had a sitting DBP of >95 and	N=65 12 weeks	Primary: Response rates, changes in sitting BP Secondary: Standing BP, sitting and standing heart rate	Primary: There was not a significant difference in response rates observed between the two treatments. Both treatments significantly reduced sitting SBP (P<0.0001) and DBP (P<0.0001) throughout the trial compared to baseline, but there were no significant differences observed between the two treatments at most visits (P values not reported). At week eight, DBP was significantly lower with nebivolol (P<0.05). Secondary: There was not a significant difference observed between the two treatments in standing BP measurements (P values not reported). Both treatments significantly reduced sitting heart rate (P<0.01) throughout the trial compared to baseline, but there were no significant differences observed between the two treatments at most visits (P values not reported). At week eight, heart rates were significantly lower with nebivolol (P<0.05).

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	<114 mm Hg			
Wald et al[57] Lisinopril 5mg QD vs atenolol 25 mg QD vs lisinopril 5 mg plus atenolol 25 mg QD vs placebo	DB, DD, RCT, XO Patients ≥ 40 years enrolled in a HTN or anticoagulation clinic	N=47 16 weeks	Primary: Reduction in BP Secondary: Not reported	Primary: The mean reductions in SBP in the atenolol alone, lisinopril alone and atenolol plus lisinopril groups were 16.1, 12.5 and 22.9 mm Hg, respectively. The mean reductions in DBP in the atenolol alone, lisinopril alone and atenolol plus lisinopril groups were 9.8, 6.8 and 13.9 mm Hg, respectively. The reductions with lisinopril plus atenolol group were significantly higher than either agent as monotherapy (P<0.001). Secondary: Not reported
Karotsis et al[58] Lisinopril 10 mg QD vs chlorthalidone 12.5 mg QD vs felodipine 5 mg QD vs valsartan 80 mg QD All patients also received diltiazem 240 mg QD.	RCT Patients 25 to 79 years of age with uncontrolled HTN (average office BP >140/90 mm Hg for all or >153/85 mm Hg for diabetics or patients <65 years of age, confirmed on 2 office visits ≥1 week apart) after ≥4 weeks of OL monotherapy with diltiazem at	N=211 8 weeks	Primary: BP Secondary: Not reported	Primary: There was a significant decline in both office and home SBP and DBP during the trial with all treatments. The antihypertensive effect was more pronounced and reached significance when home BP monitoring was used in comparison to office BP without the white-coat effect (P<0.001 for all BP changes). With or without the white-coat effect, BP still declined and the differences were significant (P<0.0001 for all BP changes). Secondary: Not reported

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	240 mg QD			
Beckett et al[59] HYVET Indapamide 1.5 mg/day vs placebo Perindopril 2 to 4 mg/day or matching placebo was added if necessary to achieve the target BP of 150/80 mm Hg.	DB, MC, PC, RCT Patients ≥80 years (of age mean age 84 years) with sustained SBP ≥160 mm Hg	N=3,845 1.8 years (mean follow-up)	Primary: Fatal or nonfatal stroke Secondary: Death from any cause, death from cardiovascular causes, death from stroke	Primary: At two years, 73.4% of patients in the active-treatment groups were receiving indapamide plus perindopril. Mean BP while sitting was 15.0/6.1 mm Hg lower with active-treatment than placebo (no P values reported). Active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% CI, –1 to 51; P=0.06). Secondary: Active treatment was associated with a 21% reduction in the rate of death from any cause (95% CI, 4 to 35; P=0.02), a 23% reduction in the rate of death from cardiovascular causes (95% CI, –1 to 40; P=0.06) and a 39% reduction in the rate of death from stroke (95% CI, 1 to 62; P=0.05). Active treatment was associated with a 64% reduction in the rate of heart failure (95% CI, 42 to 78; P<0.001). Fewer serious adverse events were reported in the active-treatment group (358 vs 448; P=0.001).
Williams et al[60] (PRISMA I and PRISMA II pooled analysis) Ramipril 2.5 mg QD for 2 weeks then force titration to 5 mg QD for 6 weeks then 10 mg QD for 6 weeks vs telmisartan 40 mg QD for 2 weeks then force titration to 80 mg QD for 12 weeks	Blinded endpoint, OL, PRO, RCT (PROBE) Patients ≥18 years of age with mild- to moderate HTN	N=1,613 14 weeks	Primary: Change from baseline in mean ambulatory BP during the final six hours of the 24-hour dosing interval Secondary: Change from baseline in mean ambulatory BP during the 24-hour dosing interval,	Primary: A significantly greater reduction in mean ambulatory BP during the last six hours of the 24-hour dosing interval was observed with telmisartan 80 mg group compared to ramipril 5 and 10 mg (P<0.0001). Secondary: Significantly greater reductions in mean 24-hour, morning, daytime, nighttime and 24-hour BP load were observed with telmisartan 80 mg compared to ramipril 5 and 10 mg (P<0.0001). Significantly greater reductions in treatment response and BP control rates were observed with telmisartan 80 mg compared to ramipril 5 and 10 mg (P<0.0001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			morning, daytime and nighttime ambulatory BP, 24-hour BP load, treatment response, BP control	
Tytus et al[61] TRAIL Trandolapril 1 to 4 mg/day At 14 weeks after treatment initiation, subjects not achieving BP targets could receive a combination of trandolapril 4 mg/day plus verapamil 240 mg/day with or without a diuretic.	MC, OL, PRO Patients (mean 56.6 years of age) with stage 1 or 2 HTN who were treatment naïve (82%) or uncontrolled on a diuretic (11%) or calcium-channel blocker (7%); uncontrolled HTN was defined as ≥140/90 mm Hg in subjects with no other risk factors or ≥130/80 mm Hg in subjects with diabetes or kidney disease	N=1,683 26 weeks	Primary: Percentage of patients reaching target BP at 14 weeks Secondary: Percentages of subjects with stage 1 and 2 HTN who achieved target BP, percentages of subjects who achieved a drop in SBP of ≥20 mm Hg and/or DBP ≥10 mm Hg, absolute changes in SBP and DBP, adverse events	Primary: At 14 weeks of treatment, 71.2% of patients who were treated with trandolapril monotherapy reached SBP/DBP <140/90 mm Hg. Secondary: At 26 weeks, 73.4% of patients achieved a target level of SBP/DBP <140/90 mm Hg. Of the 683 subjects with stage 2 HTN, 64.6% achieved the target level after 14 weeks of trandolapril and 67.9% after 26 weeks. At 14 weeks, 78.8% of subjects treated with a trandolapril regimen experienced a decrease in SBP of ≥20 mm Hg or a decrease in DBP of ≥10 mm Hg. Statistically significant (P<0.001) and clinically relevant mean decreases in SBP of –16.1 mm Hg and in DBP of –8.8 mm Hg were observed from four weeks of treatment onward for the overall study population. The mean reductions in SBP and DBP were –21.5 and –11.9 mm Hg, respectively at 14 weeks (P<0.001), and –22.4 and –12.7 mm Hg, respectively, at 26 weeks (P<0.001). A total of 343 predominantly mild, nonserious adverse events were attributed to the study drugs, reported by 15.3% of the 1,650 subjects. The most frequently reported nonserious adverse events were cough (6.3%); gastrointestinal disorders (2.3%), predominantly nausea; and headache (2.1%). No serious adverse events were attributed to the study treatment.
Tytus et al[62] MAVIKtory	MC, OS Patients with	N=8,787 6 months	Primary: Proportion of patients reaching	Primary: The target of <140/90 mm Hg was achieved by 67.3% of patients. The lower mean target of 133.4/83.3 mm Hg for nondiabetic patients and 128.6/79.3 mm

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Trandolapril 1 to 2 mg/day With or without existing antihypertensive therapy.	HTN		blood pressure targets, safety Secondary: Not reported	Hg for diabetic patients were achieved by 52.2%. Mean reductions from baseline to trial end were 19.4 mm Hg (95% CI, -19.9 to -19.0) in SBP and 10.1 mm Hg (95% CI, -10.4 to -9.8) in DBP. Cough was the most commonly reported adverse event (4.2%). Secondary: Not reported
Pauly et al[63] Trandolapril 4 mg QD vs captopril 50 mg BID If BP was not normalized at 8 weeks, HCTZ 25 mg was added.	DB, MC, RCT Patients between 21 and 65 years of age with mild-to-moderate essential HTN (DBP of 95 to 115 mm Hg)	N=180 16 weeks	Primary: Morning pre-dosing supine DBP at eight weeks of monotherapy Secondary: Supine SBP at eight weeks of monotherapy, BP at 16 weeks of therapy (including eight weeks of monotherapy and eight weeks of combination therapy with HCTZ)	Primary: Significantly greater mean reductions in supine DBP in the trandolapril group vs captopril group were observed after eight weeks of monotherapy (–13.5 vs –10.1 mm Hg; P=0.007). Secondary: Differences in supine SBP between treatment groups approached significance after eight weeks of monotherapy (P=0.06). Both SBP and DBP were significantly reduced at all time points compared to baseline for both treatment groups at the end of the study (P<0.05). The proportion of patients whose BP normalized (supine and standing BP ≤160/90 mm Hg) at the end of the study was 61% for trandolapril and 44% for captopril (P=0.02). The overall proportion of responders (DBP fell by ≥10 or to <90 mm Hg) was significantly greater in the trandolapril group (77%) than in the captopril group (58%; P<0.007).
Vaur et al[64] Trandolapril 2 mg QAM vs enalapril 20 mg QAM	DB, RCT Patients between 18 to 70 years of age with mild-to-moderate primary HTN	N=88 3 weeks	Primary: 24-hour ambulatory SBP and DBP over an active 24-hour period and subsequent 24-hour period (to	Primary: Both trandolapril and enalapril showed similar reductions in SBP and DBP over the 24-hour period. In the trandolapril group, SBP and DBP decreased from 148/92 to 135/83 mm Hg (P<0.001). In the enalapril group, SBP and DBP decreased from 143/91 to 133/83 mm Hg (P<0.001). The trough/peak ratio on active treatment was 90% (SBP) and 54% (DBP) in the trandolapril group and 49% (SBP and DBP) in the enalapril group.

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			mimic a missed dose) Secondary: Not reported	Following the missed dose, trough/peak ratio decreased to 58% (SBP)/36% (DBP) for trandolapril and 10% (SBP)/19% (DBP) for enalapril. The BP control was better sustained with trandolapril, such that significant falls in BP were observed during the daytime, nighttime and early morning periods after a missed dose, whereas during the same periods, enalapril only significantly reduced BP in the daytime period. Secondary: Not reported
Van Bortel et al[65] ACE inhibitor, ARB, β-blocker, CCB or placebo vs nebivolol	MA 12 RCTs involving >25 patients with essential HTN where nebivolol 5 mg QD was compared to placebo or other active drugs for >1 month	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; P=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; P=0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; P=0.283), CCBs (OR, 1.19; 95% CI, 0.83 to 1.70; P=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; P=0.212). Overall, a higher percentage of patients obtained normalized BP with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; P=0.012). A higher percentage of patient receiving nebivolol obtained normalized BP compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; P=0.004) and CCBs (OR, 1.96; 95% CI, 1.05 to 1.96; P=0.024), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; P=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; P<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; P=0.482). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; P=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; P=0.007) and CCBs (OR, 0.49; 95% CI 0.33 to 0.72; P<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08). Secondary: Not reported

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Wiysonge et al[66] Other antihypertensive therapies (i.e., placebo, diuretics, CCBs or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol* or propranolol)	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to CCBs (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to CCBs (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), CCBs (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of CCBs (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to CCBs (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.

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Hannson et al[67] STOP-2 Conventional group: atenolol 50 mg QD plus HCTZ 25 mg QD in combination with either amiloride 2.5 mg QD, metoprolol 100 mg QD or pindolol 5 mg QD vs newer drug group: ACE inhibitors (enalapril 10 mg QD or lisinopril 10 mg QD) or calcium antagonists (felodipine 2.5 mg QD or isradipine 2 to 5 mg QD)	BE, MC, OL, RCT Patients 70 to 84 years of age with treated or untreated essential HTN (SBP ≥180 mm Hg, DBP >105 mm Hg or both) on 3 separate occasions	N=6,614 60 months	Primary: Combined fatal stroke, MI and other fatal cardiovascular disease, combined fatal and nonfatal stroke, MI and other cardiovascular mortality Secondary: Not reported	Primary: The combined fatal mortality endpoints occurred in 221of the 2,213 patients receiving conventional therapy and in 438 of 4,401 patients receiving newer drugs (RR, 0.99; 95% CI, 0.84 to 1.16; P=0.89). The combined fatal and nonfatal mortality endpoints occurred in 460 patients receiving conventional therapy and in 887 patients receiving newer drugs (RR, 0.96; 95% CI, 0.86 to 1.08; P=0.49). Secondary: Not reported
Lindholm et al[68] β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol or propranolol) vs other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide, captopril,	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first line treatment (in ≥50% of all patients in one treatment group)	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diltiazem, enalapril, felodipine, HCTZ, isradapine, lacidipine, lisinopril, losartan or verapamil) or placebo	and outcome data for all-cause mortality, cardiovascular morbidity or both			Secondary: Not reported
Baguet et al[69] Antihypertensive drugs (enalapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.	MA Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP Secondary: Not reported	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), CCBs (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), CCBs (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not reported). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. CCBs: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to -10.9), respectively. Secondary: Not reported
Diabetes/Diabetic Nephropathy/Renal Dysfunction				
Hou et al[70] ROAD Benazepril 10 mg/day vs individual uptitration (10 to 40 mg/day with median dose of 20 mg/day) or losartan 50 mg/day vs individual uptitration (50 to 200 mg/day with median dose of 100 mg/day) Uptitration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained.	OL, PRO, RCT Patients aged 18 to 70 years with proteinuria and chronic renal insufficiency who did not have diabetes	N=360 3.7 years (median follow-up)	Primary: Time to composite of doubling of serum creatinine, ESRD or death Secondary: Changes in level of proteinuria, rate of progression of renal disease	Primary: Compared to the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through uptitration were associated with a 51 and 53% reduction in the risk for the primary end point (P=0.028 and P=0.022, respectively). There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages (no P values reported). Secondary: Optimal antiproteinuric dosages of benazepril and losartan at comparable BP control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared to their conventional dosages. There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages (no P values reported). Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (P>0.05). There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in any of the treatment arms (no P values reported).
Barnett et al[71] DETAIL Enalapril 20 mg/day vs	DB, MC, PG, RCT Patients aged 35 to 80 years of age with type 2	N=250 5 years	Primary: Change in the GFR Secondary: Annual changes in GFR, serum	Primary: After 5 years, GFR decreased by 17.9 mL/minute/1.73 m^2 with telmisartan compared to 14.9 mL/min/1.73 m^2 with enalapril (mean difference, –3.0 mL/min/1.73 m^2; 95% CI, –7.6 to 1.6). Therefore, the changes in GFR were comparable between the groups (P value not reported).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
telmisartan 80 mg/day	diabetes and HTN		creatinine level, urinary albumin excretion, and BP; rates of ESRD and cardiovascular events; all-cause mortality	Secondary: The effects of the two agents on the secondary end points were not significantly different after five years.
Mogensen et al[72] CALM Lisinopril 20 mg QD vs candesartan 16 mg QD vs lisinopril 20 mg QD plus candesartan 16 mg QD Patients received 12 weeks monotherapy followed by an additional 12 weeks of monotherapy or combination therapy.	DB, DD, MC, PG, RCT Patients 30 to 75 years of age with HTN, type 2 diabetes, and microalbuminuria	N=199 24 weeks	Primary: BP and urine albumin creatinine ratio Secondary: Not reported	Primary: At 12 weeks, mean reductions in DBP were 9.7 (P<0.001) and 9.5 mm Hg (P<0.001), respectively, and in urine albumin creatinine ratio were 46 (P<0.001) and 30% (P<0.001) for lisinopril and candesartan, respectively. Compared to either agent alone, at 24 weeks the combination of lisinopril plus candesartan resulted in 16.3 mm Hg reduction in mean DBP vs 10.4 mm Hg for candesartan alone (P<0.001) and 10.7 mm Hg for lisinopril alone (P<0.001). The reduction in urinary urine albumin creatinine ratio with combination treatment (50%) was greater than with lisinopril alone (39%; P<0.001) and candesartan alone (24%; P=0.05). All treatments were generally well tolerated. Secondary: Not reported
DREAM Trial Investigators[73] Ramipril up to 15 mg/day vs placebo	DB, MC, PC, PRO, RCT, 2-by-2 factorial design Adults ≥ 30 years of age with impaired fasting glucose and/or impaired glucose	N=5,269 3 years (median)	Primary: Composite of newly diagnosed diabetes or death Secondary: Regression to normoglycemia, glucose levels,	Primary: The composite primary outcome did not differ significantly between the ramipril group (18.1%; HR, 0.91; 95% CI, 0.81 to 1.03; P=0.15) and the placebo group (19.5%). Secondary: Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (HR, 1.16; 95% CI, 1.07 to 1.27; P=0.001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were concurrently randomly assigned to receive either rosiglitazone or matching placebo with a 2×2 factorial design. Only the results relevant to ramipril are presented in this review.	tolerance and no previous cardiovascular disease		composite of cardiac and renal events (were not yet analyzed at the time of this publication)	At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group than in the placebo group (P=0.07), though plasma glucose levels two hours after an oral glucose load were significantly lower in the ramipril group (P=0.01).
GISEN Group[74] REIN Ramipril 1.25 mg/day vs placebo	DB, PC, RCT Patients between 18 and 70 years of age who were either normotensive (<140/90 mm Hg) or hypertensive with chronic nephropathy and persistent proteinuria, who had not received ACE inhibition therapy for at least 2 months	N=166 (stratum 2) 16 months	Primary: Rate of GFR decline, extent to which this effect was dependent on the drug's antiproteinuric effect Secondary: BP control, time to doubling of baseline serum creatinine or progression to end-stage renal failure, cardiovascular complications, total and cardiovascular mortality	Primary: Mean rate of GFR decline per month was significantly lower in the ramipril group than in the placebo group (0.53 mL/minute vs 0.88 mL/minute; P=0.03). Among the ramipril-assigned patients, percentage reduction in proteinuria was inversely correlated with decline in GFR (P=0.035) and predicted the reduction in risk of doubling of baseline creatinine or end-stage renal failure (18 ramipril vs 40 placebo; P=0.04). Secondary: BP control and the overall number of cardiovascular events were similar in the two treatment groups. Fifty-eight patients (18 in the ramipril group and 40 in the placebo group) reached the combined end point of doubling of baseline serum creatinine concentration or end-stage renal failure (P=0.02). The risk of progression was still significantly reduced after adjustment for changes in SBP (P=0.04) and DBP (P=0.04) with ramipril, but not after adjustment for changes in proteinuria. Note: Originally, 352 patients were placed into stratum 1 (urinary protein excretion exceeding 1.0 g/24 hours) or stratum 2 (urinary protein excretion exceeding 3.0 g/24 hours). At the second planned interim analysis, the difference in decline in GFR between the ramipril and placebo groups in stratum 2 was highly significant (P=0.001). The Independent Adjudicating Panel therefore decided to open the randomization code and do the final analysis in this stratum while stratum 1 continued in the trial.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wright et al[75] AASK Ramipril 2.5 to 10 mg/day vs amlodipine 5 to 10 mg/day vs metoprolol 50 to 200 mg/day	DB, MC, RCT, three-by-two, factorial trial Patients were self-identified African Americans 18 to 70 years of age with HTN and a GFR between 20 and 65 mL/minute/ 1.73 m^2 and no other identified cause of renal insufficiency	N=1,094 3 to 6.4 years	Primary: Rate of change in GFR (grouped by usual BP [MAP goal 102 to 107 mm Hg] vs lower BP [≤92 mm Hg]) Secondary: Clinical composite outcome (reduction in GFR by 50% or more, ESRD, or death)	Primary: No significant difference in primary outcome was reported between the usual BP group compared to the lower BP group (P=0.24). None of the drug group comparisons showed consistently significant differences in the GFR slope. Secondary: The lower BP goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower BP group, 2%; 95% CI, –22 to 21; P=0.85). Ramipril resulted in significant risk reductions in the clinical composite outcomes compared to amlodipine (38%; 95% CI, 14 to 56; P=0.004) and metoprolol (22%; 95% CI, 1 to 38; P=0.04). There was no significant difference in the clinical composite outcome between the amlodipine and metoprolol groups.
Ruggenenti et al[76] BENEDICT Trandolapril 2 mg/day vs verapamil SR 240 mg/day vs trandolapril 2 mg/day plus verapamil SR 180 mg/day vs placebo	DB, MC, RCT Patients ≥40 years of age with type 2 diabetes (not exceeding 25 years) and HTN (SBP ≥130 mm Hg and/or DBP ≥85 mm Hg) but with normo-albuminuria (urinary albumin excretion rate of <20 µg/minute)	N=1,204 3.6 years (median)	Primary: Development of persistent microalbuminuria 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 verapamil plus trandolapril and placebo (P=0.01). Secondary: The primary outcome was reached in 6.0% of patients receiving trandolapril, 11.9% receiving verapamil and 10.0% receiving placebo (no P values reported). The estimated acceleration factor was 0.47 for trandolapril vs placebo (P=0.01) and 0.83 for verapamil vs placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Throughout the study the average trough SBP/DBP was 139/80 mm Hg for patients receiving trandolapril plus verapamil, 139/81 mm Hg for trandolapril, 141/82 mm Hg for verapamil and 142/83 mm Hg for placebo. The comparison was significant (P≤0.002) between trandolapril plus verapamil or trandolapril alone vs placebo, but not for verapamil vs placebo. Serious adverse events were similar in all treatment groups.
Casas et al[77] ACE inhibitor or ARBs compared to placebo vs ACE inhibitor or ARBs compared to other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) Specific agents and doses were not specified.	MA of RCT (searched up to January 2005), parallel-design Studies in adults that examined the effect of any drug treatment with a BP lowering action on progression of renal disease	N=127 studies 4.2 years (mean)	Primary: Doubling of serum creatinine, and ESRD Secondary: Serum creatinine, urine albumin excretion and GFR	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR (no P value reported). Conclusion: Benefits of ACE inhibitors or ARBs on renal outcomes compared to placebo are probably due to a blood-pressure lowering effect. In diabetic patients, additional renoprotective effects of ACE inhibitors or ARBs beyond BP lowering remain unproven and there is uncertainty about the greater renoprotection seen in nondiabetic renal disease.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Strippoli et al[78] ACE inhibitors vs placebo (36 trials; benazepril 10 mg/day, captopril 37.5 to 100 mg/day, cilazapril* 2.5 to 5 mg/day, enalapril 5 to 40 mg/day, fosinopril 10 mg/day, imidapril* 5 mg/day, lisinopril 2.5 to 20 mg/day, perindopril 2 to 8 mg/day and ramipril 1.25 to 10.0 mg/day) or ARBs vs placebo (4 trials; irbesartan 75 to 300 mg/day [2 trials] and losartan 50 to 100 mg/day [2 trials]) or ACE inhibitors vs ARBs (3 trials; enalapril 5 to 10 mg/day vs losartan 50 mg/day [2 trials] and captopril 75 mg/day vs valsartan 80 to 160 mg/day)	MA of 43 RCT (to September 2003) Patients with diabetic nephropathy	N=43 trials Duration at least 6 months, range 6 to 63.6 months	Primary: All-cause mortality, renal outcomes (ESRD, doubling of serum creatinine, microalbuminuria to macroalbuminuria) Secondary: Not reported	Primary: ACE inhibitors significantly reduced all-cause mortality compared to placebo or no treatment (RR, 0.79; 95% CI, 0.63 to 0.99; P=0.04). There was a nonsignificant trend for reduction in ESRD (P=0.07) and doubling of serum creatinine (P=0.08) with ACE inhibitors compared to placebo or no treatment. ACE inhibitors significantly reduced the risk of progression from microalbuminuria to macroalbuminuria (P=0.0007) and increased regression back to normoalbuminuria (P<0.0001) compared to placebo or no treatment. ARBs did not significantly reduce all-cause mortality compared to placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17; P=0.95). ARBs significantly reduced the risk of ESRD (P=0.001) and doubling of serum creatinine (P=0.004). ARBs significantly decreased the risk of progression to macroalbuminuria (P=0.001) and increased regression to normoalbuminuria (P=0.02) compared to placebo or no treatment. The three trials that compared ACE inhibitors to ARBs did not report on all-cause mortality, ESRD or doubling of serum creatinine. Progression from microalbuminuria to macroalbuminuria was reported in one trial (N=92) and there was no significant difference in risk, with the point estimate favoring ACE inhibitors (RR, 0.16; 95% CI, 0.02 to 1.44; P value not reported). Regression from microalbuminuria to normoalbuminuria in one trial showed a nonsignificant difference in the risk (P value not reported). Secondary: Not reported
Strippoli et al[79] ACE inhibitors vs placebo (38 trials)	MA of 49 RCT (to December 2005) Patients with	N=12,067 Duration at least 6	Primary: All-cause mortality, ESRD, doubling of serum creatinine	Primary: There was no significant difference in the risk of all-cause mortality for ACE inhibitors vs placebo or no treatment (RR, 0.91; 95% CI, 0.71 to 1.17) and ARBs vs placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17). No

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or ARBs vs placebo (4 trials) or ACE inhibitors vs ARBs (7 trials)	diabetic kidney disease	months	concentration, progression from micro- to macroalbuminuria, regression from micro- to normoalbuminuria, drug-related toxicity (including cough, headache, hyperkalemia, impotence and pedal edema) Secondary: Not reported	statistically significant reduction in the risk of all-cause mortality was found in the 3 studies that compared ACE inhibitors with ARBS (RR, 0.92; 95% CI, 0.31 to 2.78). A subgroup analysis of studies showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACE inhibitors (RR, 0.78; 95% CI, 0.61 to 0.98) but not when using half or less than half the maximum tolerable dose of ACE inhibitors (RR, 1.18; 95% CI, 0.41 to 3.44). There was a significant reduction in the risk of ESRD with ACE inhibitors and ARBS compared to placebo or no treatment (RR, 0.60; 95% CI, 0.39 to 0.93 and RR, 0.78; 95% CI, 0.67 to 0.91, respectively). There was a significant reduction in the risk of doubling of serum creatinine concentration with ACE inhibitors and ARBS (RR, 0.68; 95% CI, 0.47 to 1.00 and RR, 0.79; 95% CI, 0.67 to 0.93, respectively). ACE inhibitors and ARBS significantly reduced the risk of progression from micro- to macroalbuminuria (RR, 0.45; 95% CI, 0.29 to 0.69 and RR, 0.49; 95% CI, 0.32 to 0.75, respectively). ACE inhibitors and ARBS significantly increased the regression from micro- to normoalbuminuria compared to placebo or no treatment (RR, 3.06; 95% CI, 1.76 to 5.35 and RR, 1.42; 95% CI, 1.05 to 1.93, respectively). The seven studies that compared ACE inhibitors to ARBS did not report the outcome of ESRD or doubling of serum creatinine. Progression from micro- to macroalbuminuria and from micro- to normoalbuminuria were evaluated each in one trial and showed a nonsignificant difference in the risk between ACE inhibitors and ARBS. ACE inhibitors were associated with a significant increase in the risk of cough but not hyperkalemia, headache or impotence when compared to placebo or no treatment. ARBS were associated with a significant increase in the risk of hyperkalemia but not cough or headache compared to placebo or no treatment. Secondary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported

*Product not available in the United States.
Drug regimen abbreviations: BID=twice daily, QAM=every morning, QD=once daily, SR=sustained-release, TID=three times daily
Study abbreviations: AC=active comparator, AHR=adjusted hazard ratio, ARR=absolute risk reduction, BE=blinded endpoint, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, RRR=relative risk reduction, XO=cross-over
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ARB=angiotensin II receptor antagonist, BP=blood pressure, CAD=coronary artery disease, CCB=calcium channel blocker, CHD=coronary heart disease, CHF=congestive heart failure, DBP=diastolic blood pressure, ECG=electrocardiogram, ESRD=end-stage renal disease, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, HF=heart failure, HTN=hypertension, LVEF=left ventricular ejection fraction, MAP=mean arterial pressure, MI=myocardial infarction, MRI= magnetic resonance image, NIDDM=non-insulin dependent diabetes mellitus, NYHA=New York Heart Association, OR=odds ratio, PCI=percutaneous coronary intervention, PAD=peripheral artery disease, PVD=peripheral vascular disease, SBP=systolic blood pressure, TIA=transient ischemic attack

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Special Populations

Table 5. Special Populations[5-18]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Benazepril	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Food and Drug Administration approved for use in children ≥6 years of age.	Renal dose adjustment is required; for creatinine clearances <30 mL/min/1.73 m^2, an initial dose of 5 mg daily is recommended up to a maximum of 40 mg daily.	No dosage adjustment required.	D	Yes
Captopril	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Renal dose adjustment is required; initial dose should be reduced and titration should be slower and in smaller increments.	Not studied in hepatic dysfunction.	D	Yes
Enalapril	Safety and efficacy in elderly patients have not been established. Food and Drug Administration approved for use in children ages one month to 16 years.	Renal dose adjustment is required; for creatinine clearances <30 mL/min/1.73 m^2, an initial dose of 2.5 mg daily is recommended up to a maximum of 40 mg daily.	No dosage adjustment required.	D	Yes
Enalaprilat	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearance <30 mL/min/1.73 m^2, an initial dose of 0.625 mg every six hours.	Not studied in hepatic dysfunction.	D	Yes
Fosinopril	Safety and efficacy in elderly patients have not been established.	No dosage adjustment generally is required;	No dosage adjustment required.	D	Yes

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Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Food and Drug Administration approved for use in children ages six to 16 years weighing more than 50 kg.	however, the recommended initial dose in patients with heart failure is 5 mg daily.			
Lisinopril	Safety and efficacy in elderly patients have not been established. Food and Drug Administration approved for use in children ages six to 16 years.	Renal dose adjustment is required; for creatinine clearance ≥10 to ≤30 mL/minute, the recommended initial dose is 5 mg daily; for creatinine clearance <10 mL/minute, the recommended initial dose is 2.5 mg daily.	Not studied in hepatic dysfunction.	D	Unknown
Moexipril	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances ≤40 mL/min/1.73 m^2, an initial dose of 3.75 mg daily is recommended up to a maximum of 15 mg daily.	Not studied in hepatic dysfunction.	D	Unknown
Perindopril	Dosage adjustment is required for elderly; an initial dose of 4 mg daily in one or two divided doses is recommended; there is limited experience with doses >8 mg daily. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances <30 mL/minute, perindopril is not recommended; for less renal impairment, an initial dose of 2 mg daily is recommended and dose should not exceed 8 mg	Not studied in hepatic dysfunction.	D	Unknown

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Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		daily.			
Quinapril	Dosage adjustment is required for elderly; an initial dose of 10 mg daily is recommended. Safety and efficacy in children have not been established.	Renal dose adjustment is required; the following initial doses are recommended: for creatinine clearances of >60 mL/minute, 10 mg daily; for 30 to 60 mL/minute, 5 mg daily; for 10 to 30 mL/minute, 2.5 mg daily; for < 10 mL/minute, quinapril is not recommended.	Not studied in hepatic dysfunction.	D	Yes
Ramipril	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.	Renal dose adjustment is required; an initial dose of 1.25 mg daily is recommended up to a maximum of 5 mg daily.	Not studied in hepatic dysfunction.	D	Unknown
Trandolapril	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.	Renal dose adjustment is required; for creatinine clearances <30 mL/minute, an initial dose of 0.5 mg daily is recommended.	Hepatic dose adjustment is required; an initial dose of 0.5 mg daily is recommended.	D	Unknown

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Adverse Drug Events

Table 6. Adverse Drug Events (%)[5-18]

Adverse Event	Benazepril	Captopril	Enalapril/ Enalaprilat	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Cardiovascular										
Angina	<1	0.2 to 0.3	1.5	0.2 to 1.0	-	<1	-	<0.5	<1 to 3	-
Bradycardia	-	-	0.5 to 1.0	0.4 to 1.0	0.3 to 1.0	-	-	-	<1	0.3 to 4.7
Cardiac arrest	-	✔	0.5 to 1.0	✔	0.3 to 1.0	-	✔	-	✔	-
Cerebrovascular accident	-	✔	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	0.2	<0.5	<1	-
Chest pain	-	1	2.1	0.2 to 2.2	3.4	>1	2.4	2.4	<1	0.3 to 1.0
Hypotension	0.3	✔	0.9 to 6.7	0.2 to 4.4	1.2 to 9.7	0.5	0.3 to 1.0	2.9	0.5 to 1.0	0.3 to 1.1
Myocardial infarction	-	0.2 to 0.3	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	0.3 to 1.0	<0.5	<1	-
Orthostatic hypotension	0.4	✔	1.2 to 2.2	≤1.2 to 1.9	0.3 to 1.2	0.5	0.3 to 1.0	<0.5	2	-
Palpitations	<1	1	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	0.9 to 1.1	0.5 to 1.0	<1	0.3 to 1.0
Peripheral edema	<1	-	-	-	0.3 to 1.0	>1	-	-	-	-
Rhythm disturbances	-	✔	0.5 to 1.0	≤ 0.2 to 1.4	-	<1	-	<0.5	-	-
Tachycardia	-	1	0.5 to 1.0	0.4 to 1.0	0.3 to 1.0	-	-	0.5 to 1.0	<1	-
Central Nervous System										
Anxiety	<1	-	-	-	-	<1	0.3 to 1.0	-	<1	0.3 to 1.0
Ataxia	-	✔	0.5 to 1.0	-	0.3 to 1.0	-	-	-	-	-
Depression	-	✔	0.5 to 1.0	0.4 to 1.0	-	-	2	0.5 to 1.0	<1	-
Dizziness	3.6	-	0.5 to 7.9	1.6 to 11.9	5.4 to 11.8	4.3	8.2	3.9 to 7.7	1.9 to 4.0	1.3 to 23
Fatigue	2.4	-	0.5 to 3.0	≥1	2.5	2.4	-	2.6	2	-
Headache	6.2	-	1.8 to 5.2	≥1	4.4 to 5.7	>1	23.8	1.7	-	-
Insomnia	<1	-	0.5 to 1.0	0.2-1.0	0.3 to 1.0	<1	2.5	0.5 to 1.0	<1	0.3 to 1.0
Malaise	-	-	-	-	0.3 to 1.0	<1	0.3 to 1.0	0.5 to 1.0	<1	-
Nervousness	<1	✔	0.5 to 1.0	-	0.3 to 1.0	<1	1.1	0.5 to 1.0	<1	-
Paresthesias	<1	-	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	-	2.3	0.5 to 1.0	<1	0.3 to 1.0
Somnolence/ drowsiness	1.6	✔	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	1.3	0.5 to 1.0	<1	0.3 to 1.0
Vertigo	-	-	1.6	0.2 to 1.0	0.2	-	0.3 to 1.0	0.5 to 1.0	<1 to 2	0.3 to 1.0
Dermatologic										
Alopecia	<1	-	0.5 to 1.0	-	0.3 to 1.0	<1	-	0.5 to 1.0	-	-
Diaphoresis	<1	-	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	0.3 to 1.0	0.5 to 1.0	<1	-
Erythema multiforme	-	✔	0.5 to 1.0	-	-	-	0.3 to 1.0	-	<1	-

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Adverse Event	Benazepril	Captopril	Enalapril/ Enalaprilat	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Exfoliative dermatitis	-	✔	0.5 to 1.0	✔	-	-	✔	<0.5	-	-
Flushing	<1	0.2 to 0.5	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	1.6	-	-	-	0.3 to 1.0
Pemphigus/ pemphigoid	<1	✔	0.5 to 1.0	-	0.3 to 1.0	-	-	0.5 to 1.0	-	0.3 to 1.0
Photosensitivity	<1	✔	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	-	<0.5	-	-
Pruritus	<1	2	0.5 to 1.0	0.2 to 1.0	-	<1	0.3 to 1.0	0.5 to 1.0	<1	0.3 to 1.0
Rash	<1	4 to 7	0.5 to 1.0	0.2 to 1.0	0.01 to 1.7	1.6	2.3	1.4	<1	0.3 to 1.0
Stevens-Johnson syndrome	<1	✔	0.5 to 1.0	-	rare	-	-	-	<1	-
Urticaria	-	-	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	-	<1	<1	-
Gastrointestinal										
Abdominal pain	-	-	1.6	0.2 to 1.0	2.2	<1	2.7	1	<1	0.3 to 1.0
Anorexia	-	-	0.5 to 1.0	-	-	-	-	-	<1	-
Constipation	<1	-	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	0.3 to 1.0	0.5 to 1.0	<1	0.3 to 1.0
Diarrhea	-	-	1.4 to 2.1	>1	2.7 to 3.7	3.1	4.3	1.7	≤1	0.3 to 1.0
Dry mouth	-	-	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	0.3 to 1.0	0.5 to 1.0	<1	-
Dyspepsia	-	✔	0.5 to 1.0	-	0.3 to 1.0	>1	0.3 to 1.0	<0.5	<1	0.3 to 6.4
Hepatitis	-	✔	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	-	<0.5	<1	-
Nausea	1.3	-	1.3 to 1.4	1.2 to 2.2	2	>1	2.3	2.4	2	-
Pancreatitis	<1	✔	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	✔	<0.5	<1	0.3 to 1.0
Vomiting	<1	-	1.3	1.2 to 2.2	0.3 to 1.0	<1	1.5	2.4	2	0.3 to 1.0
Genitourinary										
Decreased libido	<1	-	-	0.2 to 1.0	0.4	-	-	-	-	0.3 to 1.0
Impotence	<1	✔	0.5 to 1.0	-	1	-	-	0.5 to 1.0	<1	0.3 to 1.0
Oliguria	-	0.1 to 0.2	0.5 to 1.0	-	0.3 to 1.0	<1	-	-	-	-
Urinary tract infection	<1	-	1.3	-	0.3 to 1.0	-	2.8	0.5 to 1.0	-	-
Musculoskeletal										
Arthralgia	<1	✔	✔	0.2 to 1.0	0.3 to 1.0	<1	0.3 to 1.0	0.5 to 1.0	<1	-
Arthritis	<1	-	✔	✔	0.3 to 1.0	-	1	-	<1	-
Muscle cramps	-	-	0.5 to 1.0	0.2 to 1.0	0.5	-	-	-	-	0.3 to 1.0
Myalgia	<1	✔	✔	0.2 to 1.0	0.3 to 1.0	1.3	0.3 to 1.0	-	<1	4.7
Respiratory										
Asthma	<1	✔	0.5 to 1.0	-	0.3 to 1.0	-	-	-	-	-
Bronchitis	<1	-	1.3	-	0.3 to 1.0	-	0.3 to 1.0	-	-	-
Bronchospasm	-	✔	0.5 to 1.0	0.2 to 1.0	0.3 to 1.0	<1	-	-	-	-

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

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

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Contraindications/Precautions[5-18]

Angiotensin converting enzyme (ACE) inhibitors are contraindicated with patients with a history of angioedema.

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 are associated with symptomatic hypotension. ACE inhibitors 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.

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.

Rarely, ACE inhibitors have been associated with cholestatic jaundice that progresses to fulminant hepatic necrosis and sometimes death.

Black Box Warning: ACE Inhibotors[5]

WARNING
Avoid Use in Pregnancy When pregnancy is detected, the angiotensin converting enzyme (ACE) inhibitors should be discontinued as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Drug Interactions

Table 7. Drug Interactions[5-18]

Drug(s)	Interaction	Mechanism
Angiotensin converting enzyme inhibitors (all)	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).
Angiotensin converting enzyme inhibitors (all)	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 inhibitors inhibitor may be reduced.
Angiotensin converting enzyme inhibitors (all)	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Angiotensin converting enzyme inhibitors may temporarily increase insulin sensitivity and increase the risk of hypoglycemia.

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Drug(s)	Interaction	Mechanism
Angiotensin converting enzyme inhibitors (all)	Indomethacin	Indomethacin inhibits prostaglandin synthesis. The hypotensive effect of angiotensin converting enzyme inhibitors may be reduced.
Angiotensin converting enzyme inhibitors (all)	Lithium	Through an unknown mechanism, angiotensin converting enzyme inhibitors may increase lithium levels, which results in neurotoxicity.

Dosage and Administration

Table 8. Dosing and Administration[5-18]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Benazepril	Hypertension: Tablet: initial, 10 mg once daily (for patients not receiving diuretics); maintenance, 20 to 40 mg/day as a single dose or in two equally divided doses; maximum, >80 mg/day has not been evaluated	Hypertension in children ≥6 years of age: Tablet: initial, 0.2 mg/kg once daily; maximum, >0.6 mg/kg (or in excess of 40 mg daily) has not been studied Note: the package insert contains information on how to compound a suspension from the tablets.	Tablet: 5 mg 10 mg 20 mg 40 mg
Captopril	Diabetic nephropathy: Tablet: maintenance, 25 mg three times daily Heart failure: Tablet: initial, 25 mg three times daily; maximum, 450 mg/day Hypertension: Tablet: initial, 25 mg two to three times daily; maintenance, after one to two weeks can increase to 50 mg two to three times daily; maximum: 450 mg/day Myocardial infarction (left ventricular dysfunction after myocardial infarction): Tablet: initial, 6.25 mg once, followed by 12.5 mg three times daily; target maintenance, 50 mg three times daily	Safety and efficacy in children have not been established.	Tablet: 12.5 mg 25 mg 50 mg 100 mg
Enalapril	Heart failure: Tablet: initial, 2.5 mg/day; maintenance, 2.5 to 20 mg two times daily; maximum, 40 mg/day in divided doses	Hypertension in children one month to 16 years of age: Solution: initial, 0.08	Solution: 1 mg/mL Tablet:

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Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertension: Solution: initial, 5 mg once daily; maintenance, 10 to 40 mg/day as a single dose or in two divided doses Tablet: initial, 5 mg once daily; maintenance, 10 to 40 mg/day as a single dose or in two divided doses Left ventricular dysfunction: Tablet: initial, 2.5 mg two times daily; target maintenance, 20 mg/day in divided doses	mg/kg (up to 5 mg) once daily; maximum, >0.58 mg/kg (or in excess of 40 mg) has not been studied Tablet: initial, 0.08 mg/kg (up to 5 mg) once daily; maximum, >0.58 mg/kg (or in excess of 40 mg) has not been studied Note: the package insert contains information on how to compound a suspension from the tablets.	2.5 mg 5 mg 10 mg 20 mg
Enalaprilat	Hypertension: Injection: Initial, 1.25 mg/dose (0.625 mg for patients on diuretics), given over five minutes every six hours; doses as high as 5 mg every six hours have been tolerated for up to 36 hours	Safety and efficacy in children have not been established.	Injection: 1.25 mg/mL
Fosinopril	Heart failure: Tablet: initial, 10 mg once daily; maintenance, 20 to 40 mg/day; maximum, 40 mg once daily Hypertension: Tablet: initial, 10 mg once daily; maintenance, 20 to 40 mg/day in a single or divided dose(s); maximum, 80 mg/day	Hypertension in children six to 16 years of age: Tablet (>50 kg): 5 to 10 mg once daily	Tablet: 10 mg 20 mg 40 mg
Lisinopril	Heart failure: Tablet: initial, 5 mg once daily; maintenance, 5 to 20 mg once daily Hypertension: Tablet: initial, 10 mg once daily; maintenance, 20 to 40 mg once daily Post-myocardial infarction: Tablet: initial, 5 mg every 24 hours for two doses, followed by 10 mg every day for six weeks	Hypertension in children six to 16 years of age: Initial: 0.07 mg/kg (up to 5 mg) once daily; doses >0.61 mg/kg (or in excess of 40 mg) have not been studied Note: the package insert contains information on how to compound a suspension from the tablets.	Tablet: 2.5 mg 5 mg 10 mg 20 mg 30 mg 40 mg
Moexipril	Hypertension: Tablet: initial, 7.5 mg once daily; maintenance, 7.5 to 30 mg/day in a single	Safety and efficacy in children have not been established.	Tablet: 7.5 mg 15 mg

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Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	or divided dose(s); maximum, 60 mg/day		
Perindopril	Cardiovascular risk reduction (coronary artery disease): Tablet: initial: 4 mg once daily for two weeks; maintenance, increase as tolerated to 8 mg once daily Hypertension: Tablet: initial, 4 mg once daily; maintenance, 4 to 8 mg/day in a single or divided dose(s); maximum, 16 mg/day	Safety and efficacy in children have not been established.	Tablet: 2 mg 4 mg 8 mg
Quinapril	Heart failure: Tablet: initial, 5 mg twice daily; maintenance, titrate at weekly intervals to 10 to 20 mg two times daily Hypertension: Tablet: initial, 10 to 20 mg once daily; maintenance, 20 to 80 mg/day in a single or divided dose(s)	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg
Ramipril	Cardiovascular risk reduction: Capsule: initial, 2.5 mg once daily for one week, followed by 5 mg once daily for three weeks; maintenance, 10 mg once daily Hypertension: Capsule: initial, 2.5 mg once daily; maintenance, 2.5 to 20 mg/day in single or divided dose(s) Post-myocardial infarction (heart failure after myocardial infarction): Capsule: initial, 2.5 mg twice daily; target maintenance, 5 mg twice daily	Safety and efficacy in children have not been established.	Capsule: 1.25 mg 2.5 mg 5 mg 10 mg Tablet: 1.25 mg 2.5 mg 5 mg 10 mg
Trandolapril	Post-myocardial infarction (left ventricular dysfunction or heart failure after myocardial infarction): Tablet: initial, 1 mg once daily; maintenance, titrate as tolerated to target of 4 mg once daily Hypertension: Tablet: initial, 1 mg once daily in non-African American patients and 2 mg once daily in African American patients; maintenance, 2 to 4 mg once daily	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 4 mg

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that guidelines addressing the treatment of hypertension and stable angina are presented globally, addressing the role of various medication classes in the treatment of these diseases. Due to the complexity of treatment regimens for unstable angina,

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acute coronary syndromes, myocardial infarction and heart failure, the associated guideline summaries focus on the role of the angiotensin converting enzyme inhibitors in disease management.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[80]	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease should be treated with blood pressure medication(s) as tolerated, including angiotensin-converting enzyme inhibitors (ACE inhibitors) and/or β-adrenergic blocking agents (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction and have a LVEF of ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-myocardial infarction without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Management of Stable Angina Pectoris (2006)**[81]	Therapy to improve prognosis • Aspirin 75 mg once daily is recommended in all patients without contraindications. • Statin therapy is recommended for all patients with coronary disease. • ACE inhibitor therapy is recommended for patients with indications for ACE inhibition including hypertension, heart failure, left ventricular

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Clinical Guideline	Recommendation
	dysfunction and history of myocardial infarction with left ventricular dysfunction and diabetes. • β-blocker therapy is recommended in patients with history of myocardial infarction or heart failure. • Class IIa evidence includes ACE inhibition in patients with angina and proven coronary disease, clopidogrel in patients with stable angina who are not candidates for aspirin and high dose statin therapy in high risk patients with proven coronary disease. • Class IIb evidence includes fibrates in patients with low high density lipoprotein cholesterol and high triglycerides who have diabetes or metabolic syndrome. • Calcium channel blockers may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction and who do not have heart failure. <u>Therapy to improve symptoms and/or reduce ischemia</u> • Short-acting nitroglycerin therapy is recommended for acute symptom relief and situational prophylaxis. • Test the effects of a β-1 blocker and titrate to full dose; consider the need for 24-hour protection against ischemia. • If β-blockers are not effective or not tolerated, attempt monotherapy with a calcium channel blocker, long-acting nitrate or nicorandil*. • If the effects of β-blocker therapy are insufficient, add a dihydropyridine calcium channel blocker. • Class IIa evidence includes a sinus node inhibitor in the case of β-blocker intolerance, or a long-acting nitrate or nicorandil* in place of a calcium channel blocker in the case of insufficient response to calcium channel blocker monotherapy or combination therapy with a calcium channel blocker and β-blocker. • Class IIb evidence includes the use of metabolic agents where available as add-on therapy or in place of conventional therapy when conventional therapy is not tolerated. <u>Treatment of syndrome X</u> • Therapy with nitrates, β-blockers and calcium channel blockers alone or in combination is recommended. • Statin therapy is recommended in patients with hyperlipidemia. • ACE inhibitors are recommended in patients with hypertension. • Class IIa evidence includes a trial of other anti-anginal agents such as nicorandil and metabolic agents. <u>Treatment of vasospastic angina</u> • Treatment with calcium channel blockers is recommended in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.
American College of Cardiology/American Heart Association: **Guidelines for the Management of Patients With Unstable Angina/Non-ST-**	<u>Early hospital care-anti-ischemic therapy: continuing ischemia/other clinical high-risk features present</u> • An oral ACE inhibitor is recommended in the first 24 hours in patients with pulmonary congestion or LVEF ≤40%, in the absence of hypotension or known contraindications. • An ARB is recommended in patients intolerant to ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF

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Clinical Guideline	Recommendation
Elevation Myocardial Infarction (2011)[82]	≤40%. Long-term medical therapy and secondary prevention: inhibition of the renin-angiotensin-aldosterone system • ACE inhibitors should be given and continued indefinitely in patients with heart failure, left ventricular dysfunction (LVEF <40%), hypertension, or diabetes, unless contraindicated. • ARBs should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and who have either clinical or radiological signs of heart failure and LVEF<40%. • ACE inhibitors are reasonable for all patients, even without left ventricular dysfunction, hypertension, or diabetes mellitus, unless contraindicated. • ACE inhibitors are reasonable for patients with heart failure and LVEF >40%. • ARBs can be useful as an alternative to ACE inhibitors in patients who are intolerant of an ACE inhibitor, provided there are either clinical or radiological signs of heart failure and LVEF <40%. • Combination ACE inhibitor and ARB therapy may be considered in patients with persistent symptomatic heart failure and LVEF <40% despite conventional therapy including an ACE inhibitor or ARB alone.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2011)[83]**	Treatment: patients with heart failure • β-blockers and ACE inhibitors/ARBs, appropriately titrated, are recommended in patients with non-ST-segment elevation acute coronary syndrome and left ventricular dysfunction with or without signs of heart failure. Long-term management: secondary prevention • ACE inhibitors are indicated within 24 hours in all patients with LVEF ≤40% and in patients with heart failure, diabetes, hypertension, or chronic kidney disease, unless contraindicated. • ACE inhibitors are recommended for all other patients to prevent recurrence of ischemic events. Preference should be given to agents and doses of proven efficacy. • ARBs are recommended for patients intolerant to ACE inhibitors. Preference should be given to agents and doses of proven efficacy.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)[84]**	Routine medical therapies: renin-angiotensin-aldosterone system inhibitors • An ACE inhibitor should be administered within the first 24 hours to all patients with ST-segment elevation myocardial infarction with anterior location, heart failure, or ejection fraction ≤40%, unless contraindicated. • An ARB should be given to patients who have indications for but are intolerant of ACE inhibitors. • ACE inhibitors are reasonable for all patients with no contraindications to their use.
American College of Cardiology/American Heart Association: **2007 Focused Update of the American College of Cardiology/ American Heart Association 2004**	Secondary prevention • Patients with comorbid hypertension should be treated initially with β-blockers and/or ACE inhibitors with the addition of other medications as needed to achieve a blood pressure goal of <140/90 mm Hg (or <130/80 mm Hg in patients with diabetes or chronic kidney disease). • ACE inhibitors are recommended in all patients with a LVEF ≤40% and those with hypertension, diabetes or chronic kidney disease, unless contraindicated.

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Clinical Guideline	Recommendation
Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)[85]	• ACE inhibitors are reasonable in patients with normal left ventricular function and well-controlled cardiovascular risk factors. • ARBs are recommended in patients who are intolerant to ACE inhibitors and have heart failure or who have a LVEF of ≤40%. • ARBs should be considered in all patients intolerant to ACE inhibitor therapy. • Combination therapy with ARBs and ACE inhibitors may be considered in patients with systolic dysfunction heart failure.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2012)**[86]	Long-term management: secondary prevention • ACE inhibitors are indicated within the first 24 hours in patients with evidence of heart failure, left ventricular systolic dysfunction, diabetes, or an anterior infarct. • An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure, left ventricular systolic dysfunction, particularly those who are intolerant to ACE inhibitors. • ACE inhibitors should be considered in all patients in the absence of contraindications.
National Institute for Health and Clinical Excellence: **Post-Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)**[87]	• All patients should be offered an ACE inhibitor early after presenting with an acute myocardial infarction. • Assessment of left ventricular function is recommended in all patients post-myocardial infarction. • All patients with preserved left ventricular function or with left ventricular systolic dysfunction should continue treatment with an ACE inhibitor indefinitely, whether or not they have symptoms of heart failure. • Routine use of ARBs after a myocardial infarction is not recommended. • ARBs may be considered alternatives in patients who are intolerant to ACE inhibitor therapy. • Combined treatment with an ACE inhibitor and an ARB is not routinely recommended. • In patients with a proven myocardial infarction in the past and with heart failure and left ventricular systolic failure, treatment should be in line with recommendations for chronic heart failure. • In patients with a proven myocardial infarction in the past and with asymptomatic left ventricular systolic dysfunction and in those without heart failure and preserved left ventricular function, ACE inhibitors are recommended (ARBs may be given to patients who are intolerant to ACE inhibitors).
American College of Cardiology/American Heart Association: **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[88] **and Diagnosis and Management of Heart Failure in Adults (2009 Focused Update)**[89]	Patients at risk for developing heart failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors and β-blockers have been shown to prevent heart failure. The ARBs, losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes mellitus and nephropathy. • Lipid disorders should be treated according to contemporary guidelines. • ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, myocardial infarction and heart failure. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left

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Clinical Guideline	Recommendation
	ventricular dysfunction or hypertension. • ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes and hypertension with other cardiovascular risk factors. Patients with cardiac structural abnormalities or remodeling who have not developed heart failure symptoms (Stage B) • β-blockers and ACE inhibitors should be used in all patients with a recent or past history of myocardial infarction. • β-blockers and ACE inhibitors should be used in patients who have reduced LVEF and do not have a history of myocardial infarction or heart failure. • ARBs are recommended for patients with reduced LVEF and a history of a myocardial infarction if they are intolerant to ACE inhibitors. • ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy. Patients with current or prior symptoms of heart failure (Stage C) • ACE inhibitors are recommended in all patients with current or past symptoms of heart failure and reduced LVEF, unless contraindicated. • ARBs are recommended in all patients intolerant to ACE inhibitors with current or past symptoms of heart failure and reduced LVEF. • ARBs are reasonable alternatives to ACE inhibitors as first-line therapy in patients with mild-to-moderate heart failure and reduced LVEF. • The addition of an ARB is reasonable in patients who are symptomatic despite conventional treatment. • The routine use of a combination of an ACE inhibitor, ARB and aldosterone antagonist is not recommended. Patients with heart failure and normal LVEF • β-blockers, ARBs, ACE inhibitors and calcium channel blocker may be useful in patients with heart failure and controlled hypertension to improve symptoms.
Heart Failure Society of America: **2010 Comprehensive Heart Failure Practice Guideline (2010)**[90]	Patients at risk for development of heart failure • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with coronary artery disease, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. Patients with asymptomatic heart failure and reduced LVEF • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. Patients with left ventricular systolic dysfunction • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE

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	inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a myocardial infarction and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a myocardial infarction and in patients with chronic heart failure and systolic dysfunction. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a myocardial infarction. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-myocardial infarction with reduced LVEF or heart failure. <u>Managing patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists and isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing calcium channel blocker (amlodipine) may be considered. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction.

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	• ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2012)**[91]	Treatments recommended in potentially all patient with symptomatic (New York Heart Association [NYHA] functional class II-IV) systolic heart failure
	• ACE inhibitors are recommended, in addition to a β-blocker, for all patients with an ejection fraction ≤40% to reduce the risk of hospitalization and the risk of premature death.
	• A β-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor is not tolerated), for all patients with an ejection fraction ≤40% to reduce the risk of heart failure hospitalization and the risk of premature death.
	
	Other treatments with less-certain benefits in patients with symptomatic (NYHA class II-IV) systolic heart failure: ARBs
	• ARBs are recommended to reduce the risk of heart failure hospitalization and the risk of premature death in patients with an ejection fraction ≤40% and unable to tolerate an ACE inhibitor because of cough.
	• ARBs are recommended to reduce the risk of heart failure hospitalization in patients with an ejection fraction ≤40% and persisting symptom (NYHA class II-IV) despite treatment with an ACE inhibitor and a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist.
	
	Recommendations for the management of ventricular arrhythmias in heart failure
	• It is recommended that treatment with an ACE inhibitor (or ARB), β-blocker, and mineralocorticoid receptor antagonist should be optimized in patients with ventricular arrhythmias.
	
	Recommendations for the treatment of hypertension in patients with symptomatic heart failure (NYHA functional class II-IV) and left ventricular systolic dysfunction
	• Step 1: one or more of an ACE inhibitor (or ARB), β-blocker, and mineralocorticoid receptor antagonist is recommended as first, second, and third line therapy, respectively, because of their associated benefits (i.e., reducing the risk of heart failure hospitalization, reducing the risk of premature death).
	• Step 2: a thiazide diuretic (or if the patient is treated with a thiazide diuretic, switching to a loop diuretic) is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), β-blocker, and mineralocorticoid receptor antagonist.
	• Step 3:
	  o Amlodipine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), β-blocker, mineralocorticoid receptor antagonist, and diuretic.
	  o Hydralazine is recommended when hypertension persists despite treatment with a combination of as many as possible of

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	an ACE inhibitor (or ARB), β-blocker, mineralocorticoid receptor antagonist, and diuretic. o Felodipine should be considered when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), β-blocker, mineralocorticoid receptor antagonist, and diuretic. Treatment of acute heart failure • An ACE inhibitor (or ARB) is recommended as soon as possible in patients with an ejection fraction ≤40%, after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure.
Eight Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[92]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.

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World Health Organization/ International Society of Hypertension: **2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)**[93]	• 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).
European Society of Hypertension/European Society of Cardiology: **2007 Guidelines for the Management of Hypertension (2007)**[94], **Reappraisal of Guidelines on Hypertension Management (2009)**[95]	• In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which must include a search for subclinical organ damage. • 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. • Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a

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	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. • 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.
National Institute for Health and Clinical Excellence: **Hypertension: The Clinical Management of Primary Hypertension in Adults (2011)**[96]	• Patients <55 years should be offered a step 1 antihypertensive with an ACE inhibitor or ARB. If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a step 1 antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker to patients >55 years of age and to black patients of African or Caribbean origin of any age. If a calcium channel blocker is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and who is stable and well controlled, continue treatment as is. • β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly: o Patients with an intolerance or contraindication to ACE inhibitors and ARBs. o Women of child-bearing potential.

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	o People with evidence of increased sympathetic drive. • If treatment is initiated with a β-blocker and a second antihypertensive is required, add a calcium channel blocker over a thiazide-like diuretic to reduce the risk of developing diabetes. • If blood pressure is not controlled with a step 1 antihypertensive, offer a step 2 antihypertensive with a calcium channel blocker in combination with an ACE inhibitor or an ARB. If a calcium channel blocker is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • For black patients of African or Caribbean origin, consider an ARB over an ACE inhibitor, in combination with a calcium channel blocker. • If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, calcium channel blocker, and a thiazide-like diuretic should be utilized. • Resistant hypertension should be considered with clinic blood pressure remains >140/90 mm Hg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a calcium channel blocker plus a diuretic. • For treatment of resistant hypertension at step 4: o Consider further diuretic therapy with low-dose spironolactone. o Consider higher-dose thiazide-like diuretic treatment. o If further diuretic therapy for resistant hypertension at step 4 is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.
American Diabetes Association: **Standards of Medical Care in Diabetes (2012)**[97]	Hypertension/blood pressure control • Pharmacologic therapy for patients with diabetes and hypertension should be a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. • If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be monitored. • ACE inhibitors and ARBs are contraindicated during pregnancy. • In children and adolescents with type 1 diabetes, ACE inhibitors should be considered for initial treatment of hypertension, following appropriate reproductive counseling due to its potential teratogenic effects. Coronary heart disease and treatment • In patients with known cardiovascular disease, consider ACE inhibitor therapy and use aspirin and statin therapy (if not contraindicated) to reduce the risk of cardiovascular events. Nephropathy screening and treatment • In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used. If one class is not tolerated, the other should be substituted. • When ACE inhibitors, ARBs, or diuretics are used, monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia. • In children and adolescents with type 1 diabetes, treatment with an ACE inhibitor, titrated to normalization of albumin excretion, should be considered when elevated albumin-to-creatinine is subsequently confirmed on two additional specimens from different days.

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Conclusions

The therapeutic class called the single entity angiotensin-converting enzyme (ACE) inhibitors is composed of 10 unique chemical entities, all of which are available generically with the exception of Epaned® (enalapril solution). All of the agents in this class are Food and Drug Administration (FDA) approved for the treatment of hypertension, and most agents are also approved for the treatment of heart failure. Evidence-based guidelines recognize the important role ACE inhibitors play in the treatment of hypertension and other cardiovascular and renal diseases. ACE inhibitors are recommended as a first-line option for patients with hypertension complicated by comorbidities, such as cerebrovascular disease, chronic kidney disease (of diabetic or nondiabetic origin), diabetes, heart failure, and myocardial infarction. ACE inhibitors are also recommended as first-line agents for patients with acute myocardial infarction, diabetic nephropathy, heart failure, and left ventricular dysfunction unless otherwise contraindicated. The current treatment guidelines do not establish a preference for one ACE inhibitor over another.

The ACE inhibitors have been shown to reduce morbidity and mortality in patients with and without hypertension. Based upon the results of the EUROPA trial, perindopril received FDA approval to reduce the risk of cardiovascular mortality and nonfatal myocardial infarction in patients with stable coronary artery diasease.[21] In the HOPE trial, ramipril reduced the risk of myocardial infarction, stroke and death from cardiovascular causes in patients 55 years and older who were at high risk of developing a major cardiovascular event and subsequently received FDA approval for this indication.[24] The SAVE trial also demonstrated a reduction in cardiovascular morbidity and mortality with captopril when compared to placebo in patients who had survived a myocardial infarction and had left ventricular dysfunction without overt heart failure.[31]

Although pharmacokinetic and pharmacodynamic differences exist between ACE inhibitors, the clinical relevance of these differences has not been established. A limited number of studies have been conducted comparing the single entity ACE inhibitors at adequate doses and duration to one another. Comparative data regarding the ACE inhibitors has not demonstrated distinct, clinically significant differences regarding efficacy, safety and tolerability. The consensus guidelines do not give preference to or distinguish one ACE inhibitor over another.

Adverse effects common to all ACE inhibitors include dry cough, angioedema, hyperkalemia, acute renal failure and hypotension, particularly after initial doses of an ACE inhibitor in hypovolemic patients.[5,6]

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