Drug Class Review on Angiotensin Converting Enzyme Inhibitors

Final Report Update 2

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The Agency for Healthcare Research and Quality has not yet seen or approved this report.

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Introduction

Angiotensin-converting-enzyme-inhibitors (ACEIs) block the activation of the renin-aldosterone system, an important mediator of blood pressure. In addition to their effects on blood pressure, ACEIs are also thought to have beneficial effects on ventricular remodeling following myocardial infarction and in patients with heart failure, and on preventing the progression of diabetic nephropathy. The American Heart Association and American College of Cardiology recommend ACEIs as standard therapy in patients with recent myocardial infarction,[1] in patients with systolic heart failure,[2] and in patients at high risk for cardiovascular events.[3] In addition, the American Diabetes Association recommends ACEIs as standard treatment for patients with diabetic nephropathy.[4]

Eleven ACEIs are marketed in North America: benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. These drugs have Food and Drug Administration (FDA) indications for treating hypertension, heart failure, secondary prevention of myocardial infarction, and diabetic nephropathy. ACE inhibitors (with the exception of captopril and lisinopril) are prodrugs requiring activation through hepatic biotransformation. Most ACEIs have half-lives of 10-12 hours; the shortest-acting are captopril (<2 hours) and quinapril (2 hours), while the longest-acting is ramipril (13-17 hours). ACEIs are eliminated mainly by the kidneys and to a lesser extent through the liver. Benazepril, captopril, enalapril, and lisinopril are less dependent on hepatic elimination than the other ACEIs. All ACEIs except fosinopril require dose adjustment in renal failure (creatinine clearance<30 ml/min).

The role of ACEIs in treating patients who have high blood pressure is evolving. In May 2003 the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) published an "express" version of their new recommendations.[5] JNC-7 recommends thiazide diuretics as the first-line option for patients with Stage-1 hypertension who do not have compelling indications for another agent. JNC-7 notes that most patients will eventually need 2 drugs to control hypertension. For patients with Stage-2 hypertension (SBP>160 or DBP>100), JNC-7 recommends starting therapy with 2 drugs, usually a diuretic plus an ACEI, beta blocker, or calcium channel blocker. ACEIs are recommended as one of several acceptable first-line options for patients who have hypertension in combination with one of the following "compelling indications": heart failure, diabetes, chronic kidney disease, high cardiovascular risk, a history of myocardial infarction, or a history of stroke.

Scope and key questions

The purpose of this review is to compare the efficacy and adverse effects of different ACEIs. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians, patients. The participating organizations approved the following key questions to guide this review.

In developing the scope and key questions, this report assumes that a clinical decision to use an ACEI has been made, and the remaining decision is which ACEI should be chosen.

We selected the following key questions to guide the review:

1. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do angiotensin converting enzyme inhibitors differ in efficacy?

2. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, nondiabetic nephropathy, or recent myocardial infarction, do angiotensin converting enzyme inhibitors differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one angiotensin converting enzyme inhibitor is more effective or associated with fewer adverse events?

Table 1. FDA indications for ACEIs

Drug	High Blood Pressure	Heart Failure or Heart Failure after MI	Recent MI	Diabetic nephropathy	Reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes.	Half-Life	Elimination
Benazepril (Lotensin)	Yes					10-11 hours**	Predominantly renal, 11%-12% biliary
Captopril (Capoten)	Yes	Yes*	Yes	Yes		<2 hours	>95% renal
Cilazapril (Inhibace, Canada)	Yes	Yes				7-11 hours	Renal
Enalapril (Vasotec)	Yes	Yes*				11 hours**	60% renal, 33% fecal
Fosinopril (Monopril)	Yes	Yes				12 hours**	50% renal, 50% fecal
Lisinopril (Prinivil, Zestril)	Yes	Yes	Yes			12 hours	No data
Moexipril (Univasc)	Yes					2-9 hours**	13% renal, 53% fecal
Perindopril (Aceon)	Yes					3-10 hours**	75% renal, 25% fecal
Quinapril (Accupril)	Yes	Yes				2 hours**	60% renal, 37% fecal
Ramipril (Altace)	Yes	Yes (HF)			Yes	13-17 hours**	60% renal, 40% fecal
Trandolapril (Mavik)	Yes	Yes (HF & LV Dysfx)				10 hours**	33% renal, 56% fecal

*Also indicated for asymptomatic LV dysfunction. HF=heart failure, LV=left ventricle, Dysfx=dysfunction
**Of active metabolite

METHODS

To identify articles relevant to each key question, we searched (in this order): the Cochrane Central Register of Controlled Trials (1st Quarter 2005), MEDLINE (1966-February Week 3 2005), EMBASE (1980-2/18/2005), Premedline (through February 24, 2005), and reference lists of review articles. In electronic searches we used broad searches, combining terms for included ACEIs with terms for relevant clinical outcomes and patient populations (see Appendix A for complete search strategy). In addition, pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 6.0).

Study selection

All English-language titles and abstracts and suggested additional citations were reviewed for inclusion, using criteria developed by the research team with input from the subcommittee. The citations were divided between two reviewers and assessed for inclusion. One reviewer then assessed for inclusion full articles, with consultation from a second reviewer where necessary.

The key questions specified the following patient *populations*: hypertension, high cardiovascular risk, recent myocardial infarction, heart failure, diabetic nephropathy, and nondiabetic nephropathy. Study populations overlap these categories. For example, many patients with hypertension also have other cardiovascular risk factors or heart failure. Many patients who have heart failure are also "recent myocardial infarction" patients; also, ACEIs are used to prevent *symptomatic* heart failure in recent myocardial infarction patients who have *asymptomatic* left ventricular systolic dysfunction.

To avoid redundancy, we defined the following categories, which we used to classify studies:

Hypertension without compelling indications. This refers to patients who have hypertension but do not have

- a history of coronary heart disease (CHD)
- other cardiovascular diseases (CVD), such as cerebrovascular (carotid) disease, peripheral vascular disease, or a history of stroke
- other risk factors for CAD/CVD, such as diabetes, smoking or hyperlipidemia
- renal insufficiency

Hypertension with compelling indications. This refers to patients with hypertension who also have one of the conditions listed above.

High cardiovascular risk. This group includes patients who have a history of CHD/CVD, or a combination of other risk factors for CHD/CVD, such as diabetes, smoking, and hyperlipidemia. These patients may or may not have hypertension as well.

Recent myocardial infarction. This group includes patients who have had a recent myocardial infarction and who have normal left ventricular function *or* asymptomatic left ventricular dysfunction.

Heart failure. This group includes patients who have symptomatic heart failure due to left ventricular systolic dysfunction, with or without hypertension.

Diabetic nephropathy. This group includes Type 1 or Type 2 diabetics who have laboratory evidence of nephropathy, such as albuminuria or decreased creatinine clearance.

Nondiabetic nephropathy. This group includes nondiabetics who have laboratory evidence of nephropathy, such as decreased creatinine clearance.

Included *interventions* were treatment with benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, perindopril, or trandolapril. Included *outcomes* varied according to the clinical condition and are listed in Table 2 below:

Table 2. Outcomes of treatment with ACEIs

Hypertension*	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure) 3. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance) 4. Quality-of-life
High cardiovascular risk	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure)
Recent-myocardial infarction	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Heart failure	1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure
Diabetic nephropathy	1. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)
Nondiabetic nephropathy	1. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)

*Trials that focused on blood pressure reduction but not on any health outcomes were excluded from the efficacy review.

In addition to these outcomes, we assessed for important adverse events associated with ACEIs including hypotension, cough, angioedema, and hyperkalemia. In some studies, only 'serious' or 'clinically significant' adverse events are reported. Some studies do not define these terms, and in others, the definitions varied.

We obtained full-text articles if the title and abstract review met the following criteria:

1. Systematic reviews of the clinical efficacy or adverse event rates of ACEIs for included clinical conditions that reported an included outcome OR
2. Randomized controlled trials that compared one of the included ACEIs to another included ACEI or large (> 100 patients) placebo-controlled trials for included clinical conditions that reported an included outcome OR
3. Randomized controlled trials and large, good-quality observational studies that evaluated adverse event rates for one or more of the included ACEIs.

Full-text articles were included in the systematic review if they met the above criteria and reported clinical efficacy or adverse event rates from specific ACEIs. While we preferred studies of longer duration, we had no lower limit on the length of follow-up, but excluded "single-dose studies" examining the effects of a single dose of medication rather than a course of treatment or studies that evaluated inpatients before hospital discharge. We excluded trials of ACEIs in combination with another cardiovascular drug when the effect of the ACEI could not be isolated.

Data abstraction

The following data was abstracted from included trials: study design, setting, population characteristics (including sex, age, race, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available and the trial did not report high overall loss to follow-up.

Validity assessment

We assessed quality of trials based on the predefined criteria listed in Appendix B. We rated the internal validity of each trial based on methods used for randomization; allocation concealment and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. External validity of trials was assessed based on: adequate description of the study population; similarity of patients to other populations to whom the intervention would be applied; control group receiving comparable treatment; funding source; and role of the funder.

Overall quality was assigned based on criteria developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[6, 7] Trials with a fatal flaw in one or more categories were rated poor-quality. Trials that met all criteria were rated good-quality. The remainder were rated fair-quality. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *unlikely* to be valid, while others are *probably* or *likely* to be valid. A "poor-quality" trial is not valid. The results are at least as likely to reflect flaws in the study design as they are true differences between the compared drugs. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events.

Appendix B also shows the criteria we used to rate studies reporting adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated studies as good quality for adverse event assessment if they adequately met six or more of the seven pre-defined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data synthesis

We constructed evidence tables showing study characteristics, quality ratings and results for all included studies. Poor-quality studies would usually be excluded from evidence tables, but we included them to ensure that the subcommittee is familiar with their limitations.

To assess the overall strength of evidence for a body of literature about a particular key question, we examined the consistency of study designs, patient populations, interventions, and results. Consistent results from good-quality studies across a broad range of populations suggest

a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered "good-quality.") For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

RESULTS

Overview

Searches identified 6,859 citations from electronic sources, reference lists, and pharmaceutical company submissions (Figure 1). The numbers of articles that met the inclusion criteria for each question are described below.

Most of the randomized trials had fair or good internal validity, but their applicability to community practice was difficult to determine. The treatment and control groups generally received other standard therapies for the condition evaluated, but current therapies varied depending on the date of publication and local practices. Most studies did not report numbers of patients screened or eligible for treatment. Most trials excluded patients with significant co-morbid medical conditions or 'compelling' indications or contraindications for ACEI therapy, and one trial reported that excluded patients had significantly worse outcomes than enrolled patients.[8] Some studies did not state the source of funding, but almost all that reported funding sources were funded at least in part by the pharmaceutical industry.

Key Question 1: For adult patients with various indications, do angiotensin converting enzyme inhibitors differ in efficacy?

1a 1. Hypertension without compelling indications

Mortality and cardiovascular events. A comprehensive meta-analysis published in 2003 identified 42 controlled trials of anti-hypertension drugs reporting major cardiovascular disease end points and all-cause mortality.[9] Nine trials, listed in Table 3, involved an ACEI.[10-22] The first 4 studies in Table 3 compared an ACEI (captopril, enalapril, or lisinopril) with diuretics or beta-blockers in hypertensive patients. ALLHAT, the largest trial, found no difference between chlorthalidone, amlodipine, or lisinopril, (10 to 40 mg) in the combined outcome of fatal coronary disease and nonfatal myocardial infarction, or in all-cause mortality.

As a group, these studies do not provide useful information to compare the effectiveness of different ACEIs in patients who have high blood pressure and no compelling indications.

Development of Diabetes. *Post-hoc* subanalyses from SOLVD (enalapril),[23] HOPE (ramipril),[24] ALLHAT (lisinopril),[12] and CAAPP (captopril)[25] provide strong evidence that ACEIs delay or prevent the development of diabetes, particularly in patients who have glucose intolerance.[23, 24]

The DREAM (Diabetes REduction Approaches with ramipril and rosiglitazone Medications) trial, currently in progress, will evaluate the effectiveness of ramipril and

rosiglitazone for the prevention of diabetes in over 5,000 patients with impaired glucose tolerance. This is the first study of an ACE inhibitor prospectively designed to evaluate the development of diabetes as a primary endpoint.[26]

Quality of Life. Two head-to-head trials reported a comprehensive, validated set of quality of life outcomes.[27,28] In one good-quality, large (n=379), 24-week head-to-head trial, blood pressure control was equivalent for captopril (25 to 50 mg twice a day) vs enalapril (5 to 20 mg twice a day) in otherwise healthy men with essential hypertension.[27] However, as measured at the end of the followup period, patients assigned to captopril had better quality-of-life than patients assigned to enalapril. A strength of this trial is that the investigators measured several aspects of quality-of-life. Because of the detailed measurement of quality-of-life, the investigators were able to determine that, among patients who had good quality-of-life prior to starting treatment with an ACEI, those taking captopril remained stable, while those taking enalapril worsened ($p<0.001$). The major weakness of the study was that results were reported as averages for the compared groups rather than as percentages that improved, remained stable, or worsened. Because of this, it is impossible to calculate a NNT from the published results, even though it is clear that the average differences between the captopril and enalapril groups was clinically significant. The rates of adverse events and withdrawals were similar for captopril and enalapril, so adverse events did not explain the differences in quality of life.

An earlier, large (n=360), good-quality, 8-week head-to-head trial found no difference in efficacy for reducing blood pressure quality of life among hypertensive men randomized to captopril, enalapril, or beta-blockers.[28] There were also no differences in quality of life between captopril, enalapril, and atenolol, all of which were better than propranolol for preserving quality of life. Because of the short followup period, these results should not be viewed as contradicting the results of the other head-to-head trial.

1a 2. Hypertension with compelling indications

Mortality and cardiovascular events. The second section of Table 3 lists 5 studies of patients who had hypertension as well as diabetes or a history of stroke. In two of the trials (ABCD[19] and FACET[20]), an ACEI (enalapril or fosinopril) was better than a calcium channel blocker to reduce the incidence of MI or the combined endpoint of MI, stroke or hospitalization for angina in patients who had diabetes and hypertension. In the next trial, a substudy of the UKPDS,[17, 18, 20] captopril was equivalent to a beta blocker in diabetics with hypertension.

PROGRESS compared perindopril to a placebo in hypertensive and non-hypertensive patients who had a history of stroke. Patients who did not have a definite indication for treatment with an ACEI (such as heart failure) were randomized to perindopril or placebo; in those who had an indication for a diuretic, perindopril plus a diuretic was compared with placebo.[29] Single-drug therapy with perindopril produced no discernable reduction in the risk of stroke in patients with hypertension versus placebo (risk difference 5%, confidence interval –19% to 23%). Results were similar in patients with and without diabetes.[30]

Patients with renal insufficiency or renal disease. A recent meta-analysis of 11 randomized controlled trials reported that ACEIs reduce the risk of end-stage renal disease in nondiabetic patients who have renal disease (0.69 (CI, 0.51 to 0.94).[31] In a placebo-controlled trial, ramipril reduced the incidence of end-stage renal disease and doubling of serum creatinine

in patients who had proteinuria from nondiabetic kidney diseases.[32, 33] The AASK trial (see Table 3) compared an ACEI, a beta blocker, and a calcium channel blocker in black patients with hypertensive kidney damage. The primary outcome measure was reduction in GFR by 50% or more (or > or =25 mL/min per 1.73 m2) from baseline, end stage renal disease (ESRD), or death. Compared with the metoprolol and amlodipine groups, the ramipril group manifested risk reductions in this clinical composite outcome measure of 22% (95% CI, 1%-38%; P =.04) and 38% (95% CI, 14%-56%; P =.004), respectively.[11]

Table 3. ACEI hypertension trials with active controls or placebo controls

Trial	Patients, Followup	ACEI(s)	Other drugs or groups	Comment
ACEI vs a diuretic or beta blocker				
AASK African American study of kidney disease and hypertension [10, 11]	African-American with hypertension and renal insufficiency. 3 years of followup	Ramipril (436 patients)	Metoprolol succinate or amlodipine besylate	Ramipril was better than metoprolol or amlodipine for the clinical composite outcome of reduction in GFR by 50% or more, ESRD, or death
ALLHAT [12]	High-risk hypertension, most previously treated, 4 to 8 years of followup.	Lisinopril, 10 to 40 mg/d (9054 patients)	Chlorthalidone or amlodipine	No difference in combined outcome of fatal coronary disease and nonfatal myocardial infarction.
Second Australian National Blood Pressure Study [13 14]	Hypertension, 65-84 years of age	Enalapril or other ACEI	HCTZ or other diuretic	ACEI were better than diuretics for CV events or all-cause mortality.
CAPPP Captopril Prevention Project [15]	Hypertension (measured diastolic blood pressure of 100 mm Hg on two occasions) 161/99	Captopril (5492 patients)	diuretics, beta-blockers	No difference in composite of myocardial infarction, stroke, and cardiovascular deaths.
STOP-2 [16]	Hypertension, large subgroups 11% had diabetes. 5 years of followup. 194/98	Enalapril 10 mg lisinopril 10 mg (total of 2205 patients)	Diuretics, beta- blockers	No differences in fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease.
UKPDS [17, 18]	Hypertension plus Type 2 diabetes. 8.4 years of followup.160/94	Captopril (400 patients)	Atenolol	No difference in macrovascular or microvascular outcomes.

Trial	Patients, Followup	ACEI(s)	Other drugs or groups	Comment
ACEI vs a calcium channel blocker				
ABCD Appropriate Blood Pressure Control in Diabetes [19]	Hypertension plus Type 2 diabetes. Five years of followup.155/98	Enalapril (233 patients)	Nisoldipine	Higher incidence of MI in the nisoldipine group.
FACET Fosinopril versus Amlodipine Cardiovascular Events Trial [20]	Hypertension plus Type 2 diabetes. 2.5 years of followup.	Fosinopril (189 patients)	Amlodipine	Fosinopril had a significantly lower risk of the combined outcome of MI, stroke, or hospitalized angina (14/189 vs. 27/191)
ACEI vs placebo				
PROGRESS perindopril protection against recurrent stroke study [21, 22]	Hypertensive and non-hypertensive patients with a history of stroke or transient ischemic attack	Perindopril alone or with a diuretic (3051 patients)	Placebo	Combination therapy reduced the risk of recurrent stroke in hypertensive patients with a history of stroke. Perindopril alone had no effect in any subgroup.

1b. High cardiovascular risk

Eleven trials of ACEIs have enrolled patients who have coronary artery disease or who have risk factors for cardiovascular disease but not hypertension.[34] One of these was PROGRESS (Table 3),[21] which enrolled some normotensive patients who had a previous stroke. In normotensive patients who received perindopril alone, there was no reduction in the risk of recurrent stroke.

The other 10 trials,[35-46] with the numbers-needed-to-treat to prevent major cardiovascular events, are described in Table 4 and in more detail in Evidence Table 1 (study characteristics) and Evidence Table 2 (quality assessment). Although all of these studies enrolled patients who were at risk for cardiovascular events, the populations varied in the magnitude of that risk.

For the most part, HOPE[35] should be viewed as a secondary prevention trial. About 80% of HOPE subjects had known cardiovascular disease, most commonly, a history of myocardial infarction. Nearly half had hypertension, and 38% had diabetes. In HOPE, ramipril reduced major cardiovascular events and all-cause mortality overall, in diabetics, non-diabetics, hypertensive patients, and non-hypertensive patients, but not in patients who had no history of cardiovascular disease. Ramipril also reduced the rate of the composite heart failure endpoint of heart failure death, heart failure requiring hospitalization, heart failure requiring an ACEI, or any reported heart failure (Relative risk 0.77; 95% CI 0.68, 0.87).[36] Reductions in risk of the individual components of the heart failure endpoint were not statistically significant. The composite endpoint occurred in 951 patients (10.2% of all randomized patients).

EUROPA, a large European trial of long-term treatment with perindopril 8 mg daily vs. placebo enrolled 12,218 patients with stable coronary artery disease.[37, 38] Compared with the HOPE sample, patients in EUROPA were lower risk: fewer had diabetes (12% vs 38%) or hypertension (27% vs 47%). After 4 years of followup, there was a reduction in the combined

endpoint of cardiovascular mortality, MI, or cardiac arrest in the perindopril group (RR=0.79, 95% CI 0.72-0.86; NNT=50), but all-cause mortality was not significantly reduced (RR 0.89; 95% CI 0.77-1.02).

Some methodological issues with EUROPA should be noted. Originally, this study was designed to last 3 years, and the primary endpoint was a composite of total mortality, MI, unstable angina, or cardiac arrest. Near the end of 3 years of followup, a decision was made to change the primary endpoint and to extend the trial by one more year. The relative risk for the original endpoint (included as a secondary endpoint) was 0.86 (95% CI 0.79-0.94) with a number needed to treat of 43 after 4 years. The EUROPA Trial had a run-in period during which all patients were given perindopril for 4 weeks; 1437 (10.5%) patients were withdrawn after the run-in. In addition to several hundred patients who did not tolerate the drug, 75 patients had a major clinical event during the run-in. If these 75 patients were included in the primary composite endpoint in the perindopril group, the NNT to prevent one cardiovascular event in 4 years would be 125.

The sponsor of EUROPA, a pharmaceutical manufacturer, had a role in the study design, interpretation of the data, writing of the report, and the decision to submit the paper for publication. The role of the funder is not described in the HOPE Trial; it was funded by both the pharmaceutical industry and other sources (e.g., the Medical Research Council of Canada).

PEACE was a large, good quality trial of trandolapril (target dose 4 mg per day) versus placebo in patients with coronary disease and normal LV function.[39, 47] There was no difference between trandolapril and placebo in the incidence of CV events or in all-cause mortality after 4.8 years. The rate of major cardiovascular events in the placebo group (9%) was similar to the rate in EUROPA and indicates a population at lower risk than that enrolled in HOPE. Most of the patients had undergone PCI and were treated aggressively with lipid-lowering therapy and other standard therapies for stable coronary disease.

DIABHYCAR[40] was a study of patients with diabetic nephropathy. It is discussed here because its primary outcome measures were mortality and cardiovascular disease. Patients (N= 4,912) with type 2 diabetes and microalbuminuria or proteinuria were randomized to low dose (1.25 mg) ramipril or placebo. Fifty-six percent of the patients had hypertension. After 3 to 6 years of followup, ramipril had no effect on cardiovascular and renal outcomes. The relative risk of the primary outcome, a composite of cardiovascular death, non-fatal MI, stroke, heart failure leading to hospital admission, and end stage renal failure was 0.97 (95% CI 0.85 to 1.11).

In the SCAT (enalapril)[42] and PART2 (ramipril)[41] trials, similar proportions of patients in the placebo group had major cardiovascular events. In SCAT, there was a statistically significant reduction in these events after 4 years (see Table 4).

A shorter-term trial, CAMELOT,[43] enrolled patients with coronary artery disease and normal blood pressure. Four percent had a history of stroke, 18% diabetes, 8% Class 4 angina (angina at any level of exertion), 28% had undergone PCI, 8% CABG, 38% had a history of MI, and 26% were current smokers. After 2 years of followup, there was a trend for fewer cardiovascular events in the enalapril group compared with placebo, but differences were not significant.

The last three studies in Table 4 enrolled patients who had undergone revasularization. QUIET,[44] an angiographic study of quinapril that followed patients for only 2 years, had low power to detect a difference in cardiovascular events (n=1,750). In a 4-year study of quinapril,[46] there was no difference on the individual endpoints CV events or mortality, but there was a significant reduction in the composite endpoint of MI, stroke, and all-cause mortality.

APRES was a small post-revascularization study[45] evaluating ramipril in patients with preoperative chronic stable angina and asymptomatic moderate left ventricular dysfunction; 27% had hypertension. There was a reduction in both cardiovascular events (NNT=8) and all-cause mortality (NNT=14) after a median followup of 33 months.

Table 4. Placebo-controlled trials of ACEI in patients with known or likely coronary disease

Trial, ACEI (total number of subjects)	Patients	Placebo group rate of major CV events	% men	Age, SBP DBP	Duration of Followup	NNT*, RR (CI) Comments
HOPE Heart Outcomes Prevention Evaluation Study Ramipril 10 mg (9,297)[35, 36]	History of CVD (80%) or diabetes (38%) plus one other risk factor (HTN—47%, High cholesterol—66%, smoking—14%). Patients with nephropathy or heart failure were excluded.	17.8%	73%	66, 139 79	5 years	**NNT=27 0.79 (0.72-0.86) Also reduced all-cause mortality (NNT=56).**
EUROPA EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease. Perindopril 8 mg (12,218)[37, 38]	65% previous MI, 55% previous revascularization, 12% diabetes, 27% hypertension, 63% hypercholesterolemia . Mean 4.2 years followup Followup was originally to be 3 years. At the end of 3 years, the definition of primary endpoint was changed and study was extended by one year.	10%	85%	60, 128 78 (after run-in)	3-6 years	**NNT=50 0.80 (0.71-0.91)** All-cause mortality RR=0.89 (0.77-1.02)
PEACE Trial Trandolapril 2 to 4 mg (8,290)[39]	Stable CAD, normal or slightly reduced LVEF.	9%	82%	64, 134 78	4.8 years	0.98 (0.86-1.13) All-cause mortality 0.89 (0.77-1.03)
DIABHYCAR (Non-insulin-dependent diabetes, hypertension, microalbuninuria or proteinuria, cardiovascular events, and ramipril) Study Low dose ramipril (1.25 mg/day) (4,912) [40]	Type 2 diabetes and microalbuminuria or proteinuria (56% had hypertension).	15.3%	70%	65, 145 82	33 months	Ramipril had no effect on cardiovascular and renal outcomes (cardiovascular death, non-fatal MI, stroke, heart failure leading to hospital admission, and end stage renal failure).

PART2 Prevention of Atherosclerosis with Ramipril 5 to 10 mg (617)[41]	History of CHD or CVD.	29.8%	82%	61, 133 79	4 years	0.83 (0.54-1.28). Trend toward reduced all-cause mortality (0.64, 0.35-1.18)
SCAT Simvastatin/ Enalapril Coronary Atherosclerosis Trial (229)[42]	CHD, normal lipid levels	25.1%	89%	61, 130 78	4 years	**0.47 (0.24-0.90) NNT=16** Too small to assess all-cause mortality.
CAMELOT Enalapril 20 mg (1,332, excluding amlodipine arm)[43]	Patients with CAD (at least 20% stenosis) and normal BP (DBP <100 mmHg with or without treatment)	23.1%	72%	57 129 77	24 months	(excluding revascularization) 0.94 (0.75-1.17) All-cause mortality 1.30 (0.47-3.56)
APRES Ramipril 5 mg (159)[45]	Patients with no prior cardiac surgery, LVEF between 0.30 and 0.50 and referred for invasive revascularization with CABG or PTCA for angina pectoris. (27% had hypertension)	23%	89%	61, NR		**NNT=8 0.44 (0.20- 0.92)** **All-cause mortality NNT=14 0.25 (0.06-0.99)**
Otsuka et al, 2004 Quinapril 10 to 20 mg (253)[46]	Patients with CAD who had been successfully treated with PCI. (46% had hypertension)	14.8%	72%	63, not reported	4.8 years	MI, stroke: 0.62 (0.24-1.63) All-cause mortality: 0.39 (0.15-1.02) **Composite: NNT=12 0.42 (0.18-0.96)**
QUIET QUinapril Ischemic Event Trial 20 mg (1,750)[44]	History of PTCA, normal lipid levels.	11.9%	82%	58, 123 74	2 years	0.88 (0.61-1.29). Too small to assess all-cause mortality.

*For all cardiovascular events combined. **BOLD** means statistically significant.
CAD= coronary artery disease. CHD=coronary heart disease. CVD=other vascular disease. RR=relative risk reduction.
CI=95% confidence interval. PTCA=percutaneous transluminal coronary angioplasty.

1c. Recent myocardial infarction

In patients who have had an MI, ACEIs are given to prevent the development or progression of heart failure and to reduce mortality.

Head-to-head trials. All-cause mortality and other outcomes were evaluated in two fair-quality head-to-head trials (Evidence Table 3).[a] The two included trials enrolled 225[49] and 212[50] patients 24 to 72 hours following onset of symptoms of myocardial infarction. Heart failure was not a requirement for entry. Both studies allowed other typical medications for myocardial infarction, and used roughly therapeutically equivalent doses of ACEI in each arm.

[a] A head-to-head trial of lisinopril vs. zofenopril was excluded because zofenopril has not been approved for use in the United States.[48] This was a good-quality trial that found no differences for mortality, severe heart failure, or other cardiovascular outcomes after 6 weeks.

One trial compared captopril 25 mg three times per day versus enalapril 5 mg three times per day for 12 months[49] and the other compared captopril 100 mg per day versus perindopril 8 mg per day for 6 months.[50] Both studies were rated fair-quality because of statistically significant (p<=0.05), potentially relevant baseline differences in intervention groups (more patients on beta-blockers in the captopril group in one trial[49] and lower Killip class in the captopril group in the other[50]). In addition, one trial had poorly described blinding methods[49] and the other was an open-label trial[50] (see Evidence Table 4 for quality assessments). One trial[49] reported pharmaceutical manufacturer sponsorship, and the other[50] did not report its funding sources.

Results are summarized in Evidence Table 5. In one study, mortality was 12% (9/75) on captopril vs. 1.3% (1/75) on enalapril after 90 days (p=0.038), and 13% (10/75) vs. 3% (2/75) (p=0.022) after 12 months.[49] In the first study,[49] the primary endpoint was LV ejection fraction, which by 6 months had improved to a similar degree for enalapril and captopril.

In the other study, by Lau, both mortality and tolerability were endpoints. Mortality was 13% (13/102) on captopril vs. 6% (7/110) on perindopril after 6 months (p=0.12), with no differences in the revascularization rate (21% vs. 20%).[50] Neither head-to-head trial reported rates of symptomatic heart failure as an endpoint.

Applicability to clinical practice was difficult to assess. In the trial that reported numbers screened and eligible, approximately one-half of eligible patients were enrolled.[49] Both trials enrolled patients in the acute phase of myocardial infarction, and may not be applicable to patients presenting later after myocardial infarction. Publication bias is a concern because there were no head-to-head trials with completely negative results.

Placebo-controlled trials. Two fair-quality systematic reviews summarized 18 trials to assess the effects of ACEIs on mortality following myocardial infarction.[51, 52] Neither review assessed the internal validity of the included trials. The trials included in the 2 previous reviews are listed in Evidence Table 6. One systematic review evaluated 15 randomized trials[49, 53-66] (n=15,104) on the effects of ACEIs given for >6 weeks shortly after acute myocardial infarction on overall mortality, cardiovascular mortality, and sudden cardiac death.[51] Several of the trials were small (fewer than 100 subjects), and one used intravenous captopril.[57] The other review evaluated four large (n>1000), short-term (4-6 weeks) placebo-controlled trials (CONSENSUS-II,[56] GISSI-3,[67] ISIS-4,[68] CCS-1[69]) of early ACEI treatment following acute myocardial infarction (n=98,496).[52] One trial (CONSENSUS II)[56] reported short- and long-term outcomes and was included in both systematic reviews. Another was a head-to-head trial, PROGRESS, which we discussed above. Neither systematic review was designed to assess the comparative efficacy of different ACEIs.

Evidence Table 7 (characteristics), Evidence Table 5 (results), and Evidence Table 8 (quality ratings) describe the trials that had 100 or more subjects and met our other inclusion criteria. In addition to the trials examined in the 2 previous reviews, we identified 2 other trials of ACEIs in recent myocardial infarction: FAMIS[70, 71] and the Shanghai Second Prevention of AMI trial[72, 73]). Both were rated fair quality. One other placebo-controlled trial evaluating zofenopril, an ACEI not currently available in the U.S., was not included.[55]

Captopril was evaluated in 6 placebo-controlled trials, and enalapril, ramipril, trandolapril, lisinopril, and fosinopril in one trial each. Odds ratios for overall mortality compared to placebo overlapped for each evaluated ACEI. No clear pattern of one ACEI being superior to any other for mortality outcomes following myocardial infarction could be seen from large placebo-controlled trials. The numbers-needed-to-treat across studies are not comparable

because the duration of followup varied and because the study populations differed in the severity of myocardial infarction; the presence or absence of left ventricular dysfunction, the dose and timing of therapy; and the use of other medications. The proportion of patients receiving thrombolytics, for example, varied between studies: 44% in TRACE (trandolapril),[53] 58% in AIRE (ramipril),[54] and about 70% in ISIS-4 (captopril),[68] GISSI-3 (lisinopril)[67] and FAMIS (fosinopril).[70, 71] The results for each ACEI are summarized below and in Table 5.

Captopril. Captopril has been demonstrated to reduce all-cause mortality and heart failure when given to recent MI patients who have asymptomatic LV dysfunction. In the SAVE trial, which was good-quality, mortality from all causes was significantly reduced in the captopril group (228 deaths/1115 patients, or 20 percent) as compared with the placebo group (275 deaths/1116 patients, or 25 percent, P = 0.019) after an average of 42 months. The number-needed-to-treat to prevent one death was approximately 20 patients.[66]

In the fair-quality Chinese Cardiac Study (CCS-1), which enrolled a broader spectrum of recent MI patients (with or without LV dysfunction), the combined end point (death + heart failure) was 1680/7468 (21.5%) in the captopril 12.5 mg tid group and 1733/7494 (23.1%) in the placebo group (p = 0.02). The effect on preventing heart failure alone was statistically significant, but the effect on mortality did not reach statistical significance (9.1% vs. 9.7%), except in the subgroup with anterior wall MI (8.6% vs 10.2%, NNT=63, P = 0.02).[69]

Captopril did not significantly reduce mortality in the ECCE trial,[58] but the trend favored captopril. In the Shanghai trial[72, 73], captopril reduced in-hospital (7% (33/478) vs. 18% (62/344); p<0.05) and 20-month mortality. In the CATS trial,[61] there was no significant difference in mortality rates after 3 months, but the number of deaths (9/149 in the captopril arm and 6/149 in the placebo arm) was small.

In the short-term ISIS-4 trial (good quality), captopril reduced mortality within 5 weeks of the onset of MI (2088/29028 (7.19%) captopril-allocated deaths vs 2231/29022 (7.69%) placebo; p = 0.02), which corresponds to an NNT of approximately 200 within one month.[68] The NNT was lower (about 100) in high-risk patients (i.e., a history of previous MI or with heart failure). In this trial ACEI treatment was given for 4 weeks and then stopped. The mortality advantage disappeared after additional followup, suggesting that ACEIs started after MI should be continued for months, if not years, afterward.

Enalapril. As noted above, enalapril had an unexpected mortality advantage over captopril in a small, fair-quality head-to-head trial (PRACTICAL).[49] In placebo-controlled trials, however, enalapril has not been shown to reduce all-cause mortality. The largest trial, CONSENSUS-2, failed to show an advantage for enalapril in reducing all-cause mortality; in fact, the trend favored placebo (odds ratio 1.10, CI 0.93-1.31).[56] On the other hand, enalapril showed a significant advantage for reducing heart failure requiring a change in therapy (810/3044 (27%) vs. 908/3046 (30%); p<0.006) and a trend towards reducing heart failure requiring hospitalization (4% vs. 6%). In two smaller placebo-controlled trials listed in Evidence Table 7, the trend in mortality was also against enalapril.

Fosinopril. The FAMIS study enrolled 285 patients with acute MI and LV dysfunction.[70, 71] At 3 months, there was a trend towards higher mortality in the fosinopril arm (8.4% (11/131) vs. 5.2% (7/134). On the other hand, there was also a trend towards reduced heart failure in this group (20% vs. 24%). After 3 months, active intervention with fosinopril was discontinued and patients were followed up for 2 years on conventional therapy. After 2 years, fosinopril was associated with a significant reduction in the combined prevalence of death

or moderate-to-severe heart failure (18% vs. 27%; p=0.04) but no significant reduction in all-cause mortality was seen (14.5% fosinopril vs. 14.1% placebo).

Lisinopril. In the short-term GISSI-3 trial, lisinopril reduced mortality at 6 weeks in a very broad spectrum of acute MI patients (6.4% vs. 7.2%, p not reported).[67] The effect persisted for 6 months even though, according to the protocol, lisinopril was stopped after 6 weeks.[74] By 6 months, among patients randomized to lisinopril, 18.1% died or developed severe ventricular dysfunction versus 19.3% of those randomized to no lisinopril (NNT= 83, p = 0.03).[74]

Ramipril. In a good-quality trial (AIRE), ramipril [54] was associated with highly significant reductions in mortality (17% vs. 23%; p=0.002) and in the development of refractory heart failure (10% vs. 14%). AIRE enrolled 2,006 patients with clinical heart failure after MI. The mortality reduction persisted for several years.[75]

Trandolopril. TRACE, a good-quality trial, enrolled 1,749 patients who had left ventricular systolic dysfunction (ejection fraction less/equal 35 percent) immediately after suffering an MI.[53] Trandolapril reduced all-cause mortality (35% vs. 42%; p=0.001) as well as severe heart failure (14% vs. 20%, p=0.003). A smaller proportion of patients in TRACE received thrombolytics (44%) than in other placebo-controlled trials, making it difficult to compare its results to trials of other ACEIs.

Table 5. Placebo-controlled trials of ACEIs in patients with recent myocardial infarction

Trial (total number of subjects)	Duration of intervention	Mortality (ACEI vs. placebo)	Symptomatic heart failure (ACEI vs. placebo)	Other outcomes (ACEI vs. placebo)
Captopril				
ISIS-4 Fourth International Study of Infarct Survival (58050)[68]	4 weeks	NNT ~200 (7.19% vs. 7.69%, p=0.02)	No significant differences (17.0% vs. 17.3%)	No significant differences for re-vascularization, reinfarction, angina or stroke
CATS Captopril and Thrombolysis Study (298)[61]	3 months	Trend towards higher mortality in captopril arm (6% vs. 4%, NS)	NNT ~11 (19% vs. 28%, p=0.05)	No significant differences for re-vascularization or reinfarction
ECCE Effects of Captopril on Cardiopulmonary Exercise Parameters Study (208)[58]	4 weeks	NNT ~100 (2% vs. 3%, NS)	NNT ~9 for combined endpoint of death or symptomatic heart failure (6.7% vs. 17.3%, p=0.03)	Re-vascularization, reinfarction, angina not reported
CCS-1 Chinese Cardiac Study (6749)[69, 76]	4 weeks	NNT ~167 (9.1% vs. 9.7%, NS)	NNT ~59 (17.0% vs. 18.7%, p=0.01)	No significant differences for reinfarction, cardiac arrest, stroke
SAVE Survival and Ventricular Enlargement Study (2231)[66]	Mean 42 months	NNT ~20 (20 vs. 25%, p=0.02)	NNT ~20 for heart failure requiring open-label ACEI (11% vs. 16%, p<0.001) and NNT ~33 (14% vs. 17%, p=0.019) for heart failure requiring hospitalization	NNT ~12 for mortality or major nonfatal event (heart failure requring ACEI or hospitalization, or reinfarction) (32% vs. 40%, p<0.001)

Shanghai Second Prevention of Acute Myocardial Infarction Trial (822)[72, 73]	21-22 months	NNT ~11 for in-hospital mortality (7% vs. 18%, p<0.05)	NNT ~19 (5.5% vs. 10.9%, p not reported)	No significant differences for reinfarction or arrhythmia
VALIANT Valsartan in Acte Myocardial Infarction[77]	24.7 months	NNT X for all-cause mortality		
Enalapril				
CONSENSUS II Cooperative New Scandinavian Enalapril Survival Study II (6090)[56]	6 months	Trend towards higher mortality in enalapril arm (10.2% vs. 9.4%, NS)	NNT ~33 for heart failure requiring change in therapy (27% vs. 30%, p<0.006) and NNT ~50 for heart failure requiring hospitalization (4% vs. 6%, NS)	No significant differences for reinfarction
Fosinopril				
FAMIS Fosinopril in Acute Myocardial Infarction Study (285)[70, 71]	3 months	Trend towards higher mortality in fosinopril arm (8.4% vs. 5.2%, NS)	NNT ~25 (20% vs. 24%, NS)	NNT ~20 for ventricular arrhythmias (0.8% vs. 6.0%, p=0.02), no significant differences for reinfarction or re-vascularization
Lisinopril				
GISSI-3 Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto Miocardico (19394)[67, 74]	6 weeks	NNT ~125 (6.4% vs. 7.2%, p not reported)	No significant differences (3.9% vs. 3.7%)	NNT ~71 for combined endpoint of mortality, clinical heart failure, ejection fraction <35%, or akinesis/dyskinesis score >45% (15.6% vs. 17.0%, p=0.009), no significant differences for reinfarction, angina, re-vascularization, or stroke
Ramipril				
AIRE Acute Infarction Ramipril Efficacy Study (2006)[54, 75]	6-15 months	NNT ~17 (17% vs. 23%, p=0.002)	NNT ~25 for severe or resistant heart failure (10% vs. 14%, p not reported)	NNT ~16 for combined endpoint of mortality, severe/resistant heart failure, reinfarction or stroke (28% vs. 34%, p=0.008), no significant differences for individual outcomes of stroke or reinfarction
Trandolapril				
TRACE Trandolapril Cardiac Evaluation Study (1749)[53]	24 months	NNT ~14 (35% vs. 42%, p=0.001)	NNT ~17 for severe heart failure (14% vs. 20%, p=0.003)	No significant differences for reinfarction

1d. Heart failure

Head-to-head trials. We identified 15 head-to-head controlled trials[78-93] of the effectiveness of ACE inhibitors for heart failure (HF) (Evidence Table 9). One trial is described in 2 different publications.[84, 85] There were 12 studies of captopril, 2 of cilazapril, 6 of enalapril, 1 fosinopril, 5 lisinopril, 3 quinapril, and 1 ramipril. There were no head-to-head studies of benazepril, trandolapril, moexipril, or perindopril in patients with HF. The number of patients ranged from 13 to 315; 10 trials enrolled fewer than 200 patients. Followup periods ranged from 12 weeks to 12 months, with most (11 of 13) following patients for 12 weeks. Three studies[80, 86, 87] enrolled only patients age 65 and older, and one[84] analyzed a subgroup of patients over age 65 from a larger trial. Most trials enrolled patients with NYHA functional class II or III HF; 2 trials enrolled only more severe patients, with class III to IV HF[81, 91] or LVEF less than 30%.[88] The majority of patients in all trials were men, and only one trial[85] reported the race or ethnicity of patients.

These trials were fair to poor in quality (Evidence Table 10). Four studies were open-label trials;[80-82, 88] neither patients nor investigators were blinded to treatment assignment. All but 3 trials[80, 81, 88] were multicenter, and the 3 single center trials were open-label. In one trial[86] it is not stated whether patients were randomized to treatment. The method of randomization was described in only 2 trials.[79, 88] No report described the method of allocation concealment used. Eight studies provided information on the source of funding;[80, 83, 85, 86, 88, 90, 91] of these, 7 reported pharmaceutical company support and one[88] reported funding through a grant from the National Heart, Lung, and Blood Institute.

Mortality

Only one head-to-head trial reported mortality as a primary outcome.[90] This fair-quality study, conducted in France, compared fosinopril (5mg to 20 mg) to enalapril (also 5 mg to 20 mg) in 254 patients. Recruitment of patients was stratified to enroll at least one-third patients over age 65 (average age was 63). At 12 months of followup, 1.6% of patients randomized to fosinopril had died, compared to 4.6% of those randomized to enalapril (p-value NS, not given). The combined endpoint of total hospitalization plus death was smaller in the fosinopril group (19.7% vs 25.0%, p=0.03). Enalapril was given only once daily in this study, although large placebo controlled trials that showed a reduction in mortality with enalapril used twice-daily dosing[94, 95] and one of these[94] used a higher dose (up to 20 mg twice daily). There are no other head-to-head studies of fosinopril compared with enalapril. Nine other head-to-head trials[78, 79, 81, 84-88, 90, 92, 93, 96] reported the number of deaths that occurred during the study period (see Evidence Table 9, adverse events column), but mortality was not a primary outcome. No significant differences between ACE inhibitor groups were reported, and the numbers of deaths were too small in these studies to detect any differences if they were present.

The best evidence about the effectiveness of ACE inhibitors on mortality in patients with heart failure comes from five large placebo controlled trials discussed above in Section 1c (recent MI): SAVE (captopril), CONSENSUS (enalapril) SOLVD (enalapril), AIRE (ramipril), and TRACE (trandolapril).

A 1995 meta-analysis evaluated 32 randomized placebo-controlled trials of ACE inhibitors that measured mortality after 8 weeks or longer.[97] Results are reported in Evidence Table 11; most of the studies were small and were not designed to measure mortality as a primary outcome.

Eight of 11 ACE inhibitors had data and are included in this meta-analysis: benazepril (2 trials, 233 patients), cilazapril (1 trial, 21 patients), captopril (6 trials, 697 patients), enalapril (7 trials, 3381 patients), lisinopril (4 trials, 546 patients), perindopril (1 trial, 125 patients), quinapril (5 trials, 875 patients), and ramipril (6 trials, 1227 patients). There were no placebo-controlled trials for moexipril, fosinopril, or trandolapril at the time. This review is rated fair quality because method of quality assessment of the trials is not reported; studies with at least 8 weeks of followup that reported intention to treat results were included.

Overall, there was a significant reduction in all-cause mortality in patients allocated to an ACE inhibitor (15.8%) compared with placebo (21.9%) (OR, 0.77; 95% CI 0.67-0.88) For the combined endpoint of total mortality or hospitalization, the summary odds ratio was 0.65 (95% CI 0.57-0.74). The evidence for benazepril (2 studies), cilazapril (1 study), and perindopril (1 study) was limited, and results were statistically significant only for enalapril. However, the point estimates for captopril, ramipril, quinapril, and lisinopril were consistent with the summary odds ratio for enalapril (see Evidence Table 11), and there was no heterogeneity of effect among the ACEIs (p=0.87 for total mortality, p=0.88 for mortality plus hospitalization). Results were similar for cause-specific mortality and for trials with longer (>90 days) followup periods, but comparisons among ACE inhibitors were not made for these subanalyses.

In the TRACE trial,[8, 53] discussed above in key question 1c, trandolapril reduced mortality from heart failure in patients with recent MI.

Improvement in NYHA Class

Eleven of 15 head-to-head trials used change in NYHA functional class as an outcome measure (Table 6, below, and Evidence Table 9). In one poor-quality, open-label study from 1991,[82] there was no significant improvement from baseline in patients assigned to captopril 12.5 mg to 25 mg TID for 3 months. In all other trials, NYHA class significantly improved over the course of the trial, regardless of which ACE inhibitor patients were taking.

Three studies compared captopril to quinapril, 3 compared captopril to lisinopril, 1 compared captopril to ramipril, 1 compared captopril to cilazapril, 2 compared captopril to enalapril and 2 compared enalapril to lisinopril. In most head-to-head trials, the degree of improvement in NYHA class did not differ between the treatment groups; the ACE inhibitors examined were equally effective in improving functional class. Only 3 studies, all poor quality, open trials, reported a difference between groups in improvement in NYHA class.[80, 82, 88]

A 1991 study from The Netherlands[82] compared the effectiveness of captopril 3 times daily with enalapril once daily in patients with Class II or III HF. NYHA class was improved at 3 months in the enalapril group, but not in the captopril group. This was a small (N=52), open trial conducted at one center, and the dose of captopril (6.5 mg, 12.5 mg, or 25 mg) was lower than the dose used in other studies that found captopril to be effective in improving NYHA Class. This study was rated poor quality; it is likely that the results are due to flaws in the study's design rather than reflecting the true effectiveness of the two drugs.

Another single-center, open trial[88] compared captopril 50 mg three times daily to enalapril 20 mg twice daily for 12 weeks in 42 patients with severe HF. Seventy-one percent of patients in the captopril group versus 52% of those in the enalapril group improved by at least one NYHA Class. The number of patients in each NYHA Class at baseline is not reported. This study was also rated poor quality due to lack of blinding and small sample size. It is impossible to determine if the two groups were comparable at baseline because the severity of illness in the groups is not reported. Therefore, we cannot rule out the possibility that the greater

improvement seen in the captopril group is due to differences in the groups at baseline, rather than greater efficacy of the drug. It is also impossible to rule out bias or chance as an explanation for these results due to the lack of blinding and small sample size.

The third head-to-head study that reported a significant difference between 2 ACE Inhibitors was also a small, single-center open-label trial.[80] Only 36 of 61 patients who were enrolled were evaluated. Although improvement in a group randomized to captopril was significantly greater than in patients assigned to quinapril, these results are likely to be due to flaws in the design of the study.

No other head-to-head trial reported a difference in improvement in NYHA class when one ACE inhibitor was compared to another, and no fair-quality trial showed a difference.

Worsening Heart Failure

Only one head-to-head trial[90] reports hospitalization for deteriorating HF, the same trial that reported mortality. Event-free survival time was longer in the fosinopril group versus the enalapril group at doses of 5 to 20 mg daily. As noted in the mortality discussion above, these results may be due to an inadequate dose of enalapril given in the control group.

Five head-to-head trials reported deterioration in NYHA Class as an outcome. There were 3 comparisons of captopril versus lisinopril,[79, 85, 87] 1 comparison of captopril versus quinapril,[80] and 1 study of fosinopril versus enalapril.[89] Two studies, both comparing captopril to lisinopril, were fair quality,[85, 87] and both found no significant difference between groups in the proportion of patients who deteriorated based on the ACE inhibitor to which they were assigned (Table 6).

Table 6. Head-to-head trials of ACEIs in patients with heart failure

Study	N	Comparison	Length of follow-up	Improvement in NYHA Class	Quality Rating
Packer 1986[88]	42	Captopril vs Enalapril	12 weeks	71% vs 52%	Poor
Dirksen 1991[82]	40	Enalapril vs Captopril	12 weeks	Improvement from baseline statistically significant (p=0.02) only in enalapril group Improvement by at least 1 class: 37% vs 33% (p not reported)	Poor
Haffner 1995[86]	80	Captopril vs Enalapril	6 months	Not reported	Poor
Cilazapril-Captopril Group 1995[92, 93]	329	Cilazapril vs Captopril	6 months	Improvement by at least one class: 35% vs 36% (NS); also NS vs placebo (32%)	Fair
Bach 1992[79]	287	Lisinopril vs Captopril	12 weeks	35% vs 40% (p-values not reported)	Poor
Giles 1988, 1989[84, 85, 96]	65	Lisinopril vs Captopril	12 weeks	30% vs 31% improved (p=NS) Subgroup of patients over age 65 (Giles 1988): 24% vs 26% improved (p not reported)	Fair

Morisco 1997[87]	251	Lisinopril vs Captopril	12 weeks	37.8% vs 36.9% changes similar in both groups (no p-values reported).	Fair
Zannad 1992[89]	278	Lisinopril vs Enalapril	12 weeks	48% vs 43%(p= NS)	Poor
Zebrah Study Group (Adgey) 1993[91]	251	Lisinopril vs Enalapril	6 months	Improvement by one or more class: 68% vs 70% (p=NS)	Fair
Gavazzi 1994[83]	146	Quinapril vs Captopril	12 weeks	Improvement in NYHA class 27.1% vs 24.0% (NS)	Fair
Beynon 1997[80]	61	Captopril vs Quinapril	16 weeks after 2 to 8 weeks titration	10% vs 17% (p=0.02)	Poor
Acanfora 1997[78]	121	Quinapril vs Captopril	12 weeks	NYHA Class at Week 12: Class I 8% vs 3% (p=NS) Class II 86% vs 75% (p=NS) Class III 6% vs 22% (p<0.05)	Fair
de Graeff 1989[81]	13	Ramipril vs Captopril	12 weeks	58% vs 40% (p-value not reported)	Poor

Exercise Duration

Five head-to-head studies[78, 79, 84, 85, 89, 93] (two comparing captopril to lisinopril, one comparing captopril to quinapril, one comparing enalapril to fosinopril, and one comparing cilazapril to captopril) measured increase in exercise duration as an outcome, and 2 others (1 comparing captopril to enalapril[80] and 1 comparing captopril to quinapril[86]) measured increase in distance during a 6-minute walking test. Four of these were rated fair quality and the rest were poor.[78, 84, 85, 89, 93]

A 12-week study that enrolled 131 patients[78] found no difference in increase in exercise duration in patients taking quinapril compared with captopril (7.8 $\pm$ 1.9 seconds vs 7.1 $\pm$ 2.3 seconds, p=NS). Thirty-two percent of patients taking quinapril stopped the exercise test due to fatigue, compared with 26% of those taking captopril (p=NS).

Another study of 189 patients with HF Class II-IV,[85] no difference in the mean increase in exercise duration at week 12 in patients assigned to take lisinopril versus those assigned to captopril. In a subgroup of 65 patients over age 65,[84] there was a greater increase in exercise duration in patients taking Lisinopril (134.3 seconds vs 71.8 seconds, p=0.08). There was no difference, however, between these same groups in NYHA class, so it is not clear whether this exercise test result is clinically meaningful.

In a study that compared lisinopril with enalapril in 278 patients for 12 weeks,[89] patients in the lisinopril group increased their exercise duration by 65.1 seconds, compared with 41.9 seconds for the enalapril group (p=0.07). Before the run-in period, patients in the lisinopril group had a lower mean exercise capacity, although the difference was not significant at the end

of the run-in period. This study did not use an intention-to-treat analysis; only those patients who completed the study were analyzed. As in the other study that showed a difference in exercise duration, there was no difference between the groups in NYHA class.

The trial of cilazapril versus captopril[93] found no difference in duration of exercise testing at 24 weeks between the two treatment groups. Similarly, there was no difference in change in NYHA class.

Quality of Life

A placebo-controlled, head-to-head trial of cilazapril versus captopril[92] focused on quality of life (Evidence Table 9). On four different measures (sickness impact profile, profile of mood states, Mahler index of dyspnea-fatigue, and a health status index), there was a small improvement in quality of life after 24 weeks for both ACEI groups, but no difference between the two treatment groups. There was more improvement in ACEI groups than placebo, but the difference was not statistically significant.

1e. Diabetic and nondiabetic nephropathy

ACEIs are used in diabetics who have evidence of renal disease to prevent its progression and in diabetics who have no evidence of renal disease to prevent the development of renal disease. Our searches identified over 300 publications that addressed renal disease in diabetes. However, we did not identify any head-to-head trials of ACEIs in patients with diabetic nephropathy.

ACEIs reduce or eliminate microalbuminuria, an early sign of renal damage in diabetics (and in nondiabetics). They have also been used in patients who have frank proteinuria (> 3 gm/d) and in patients who have decreased renal function.[98]

Type 1 Diabetes. The Collaborative Study Group trial of captopril in 409 patients with Type 1 diabetes was the first study to demonstrate that an ACEI can reduce the incidence of advanced renal failure.[99] On average, the subjects had diabetes for 22 years and had close to 3 gms of proteinuria a day. The average HgbA1c was 11.7% and three-quarters had hypertension. The maximum followup period was 3 years. In this trial, compared with placebo, captopril reduced the risk of doubling of serum creatinine (NNT 10, p=0.007) and reduced the combined endpoint of death, dialysis, or transplant to a similar degree (NNT 10). The study was well-conducted, but its dramatic results apply to a small proportion of diabetics—those with longstanding, poorly controlled Type 1 diabetes, most of whom had hypertension and significant proteinuria.

Subsequently, the European Microalbuminuria Captopril Study Group[100] and the North American Microalbuminuria Study Group[101] demonstrated that, in Type 1 diabetes with microalbuminuria and without hypertension, captopril prevented the onset of clinical proteinuria and hypertension. In the NAMSG trial, creatinine clearance stayed stable in the captopril group but decreased by 10 ml/min over 2 years in the placebo group. Neither study demonstrated an effect on the risk of developing end-stage renal disease.

Lisinopril[102] and perindopril[103] also reduce urinary albumin excretion, but have not been shown to prevent the development of renal failure in Type 1 diabetics. Enalapril was equivalent to placebo and to nifedipine in a 3-year trial in normotensive Type 1 diabetics who had microalbuminuria.[104] Initially, enalapril improved urinary albumin excretion, but by 3 years there was no effect on this measure or on the development of hypertension.

Noninsulin-dependent diabetes. While ACEIs reduce albuminuria in normotensive non-insulin dependent diabetics with microalbuminuria,[105-110] they have not been shown to prevent the development of end-stage renal disease in this group.[40, 111]

Renal insufficiency or renal disease without hypertension. In a trial of 583 patients with renal insufficiency from various causes, benazepril reduced the risk of developing end-stage renal disease or a doubling of serum creatinine by approximately fifty percent.[112] At baseline, renal insufficiency was mild in 39% of all patients, and moderate in 61%. Only 21% of the subjects had diabetic nephropathy, but the effect was stronger in this subgroup than in the sample as a whole. There was only one death in the placebo group (0.4%), compared with 8 in the benazepril group (2.7%).

Key Question 2: For adult patients, do angiotensin converting enzyme inhibitors differ in safety or adverse events?

Adverse effects of ACEIs include hypotension, dry cough, angioedema, hyperkalemia, and acute renal impairment. Other adverse effects include rashes, hepatotoxicity, dysgeusia (i.e., distortions of taste), and neutropenia. The last two of these—loss of taste and neutropenia—were seen primarily with the use of high doses of captopril (e.g., >100 mg/day). Heart failure, and interactions with medicines used in heart failure, are considered to increase the risk of hypotension and acute renal impairment from ACEIs.

Angioedema (also called angioneurotic edema) is a nonpitting edema, usually involving the face, lips, tongue, or larynx, but sometimes observed in the GI tract. It is usually mild, but in severe cases it is treated with intravenous antihistamines and airway management. In a large trial of enalapril versus placebo, ACEI use increases the risk of angioedema 4-fold, from 1 per 1,000 to 4 per 1,000 among all subjects.[113] The same increase was seen in the ALLHAT study: the rate was 4 per 1,000 for lisinopril users, versus <1 per 1,000 for the other treatments.[12] In the HOPE trial, the rate of angioedema was 2 per 1,000 in the placebo group and 4 per 1,000 for ramipril users.[35]

Head-to-head trials. Twenty-four head-to-head trials compared the rates of adverse events from ACEIs available in the US. Nine of these concerned patients with hypertension,[27, 28, 114-120] two concerned recent MI patients,[49, 50] and 13 concerned patients with heart failure.

Hypertension

Two of the head-to-head trials focused on quality of life; these were described in section 1A above.[27, 28] In the remaining studies, there were no important differences in the rates of cough, angioedema, hyperkalemia, or acute renal impairment.[114-120]

Recent MI

In the two head-to-head trials (Evidence Table 12), adverse event assessment was rated fair quality.[49, 50] The quality of adverse event assessment in these two trials was lower than the quality for general internal validity (Evidence Table 4). In both trials, adverse event assessment methods were not adequately described, adverse events were not specified or pre-defined, and potential confounders were not evaluated. Withdrawals due to adverse events were not specifically reported in either trial. Although neither study found significant differences between different ACEIs for overall withdrawals, each study reported more overall withdrawals in the

group receiving captopril. In one trial, the overall withdrawal rate was 24% for captopril vs. 16% for enalapril,[49] and in the other trial, 14% for captopril vs. 9% for perindopril.[50] Neither trial reported significantly different adverse event rates for cough or symptomatic hypotension. Permanent increases in renal function were not reported in either trial. Reliable conclusions about differential safety or adverse event rates could not be drawn from head-to-head trials.

Heart failure

Evidence Table 13 shows the adverse events reported in head-to-head trials. Only one head-to-head trial was specifically designed to assess adverse events.[88] In this small (N=42), poor-quality, fixed-dose, open trial, 10% of patients taking enalapril 20 mg twice daily had first dose hypotension, and 5% had serious hypotension after 6 weeks of treatment, compared with no hypotension in patients taking captopril 50 mg three times daily. There were no withdrawals due to any adverse effects in this 12-week study, including hypotension.

In 15 head-to-head trials, the percentage of patients who withdrew due to adverse events ranged from none to 39%, and differed between groups in only one (cilazapril 5.4% vs captopril 13.0%, p-value not reported).[93] Ten studies[80-89, 93] reported the number of withdrawals due to hypotension (first dose or not), and the percentages were low in most (0%-3%). The exception was one study[86] that reported 10% withdrawals due to hypotension in the enalapril (2.5 mg twice daily) group compared with 0 in the captopril (12.5 mg twice daily) group. Doses were not titrated in this study, which may account for the high rate of hypotension.

Another study[90] reported a significantly higher occurrence of symptomatic orthostatic hypotension in patients taking enalapril 5 to 20 mg once daily compared to those randomized to fosinopril 5 to 20 mg once daily (7.6% vs 1.6%). There were no withdrawals due to hypotension in this study, and the overall withdrawal rate was similar between groups.

Six trials[78, 79, 81, 84-87] reported the number of deaths that occurred during the treatment period. There were no significant differences in the number of deaths between groups in any of these.

Placebo-controlled trials. In 12 large placebo-controlled trials of ACEIs in patients with recent myocardial infarction, adverse event assessment was fair or poor (Evidence Tables 7 and 8). In general, trials did not adequately report adverse event assessment techniques or predefine adverse events. The most consistently reported adverse event was hypotension, but definitions of 'significant' hypotension varied widely between studies. Rates of hypotension varied widely. For example, for captopril, rates of hypotension ranged from 8% to 37% in different trials. No clear pattern of one ACEI being superior to another for this adverse event could be seen in the data from these trials. Other adverse events (including cough, angioedema, significant renal failure, and withdrawal due to adverse events) were inconsistently reported, and no reliable conclusions could be drawn from these data.

A recent meta-analysis examined adverse events in 51 placebo- or standard treatment-controlled randomized trials of ACE inhibitors in patients with heart failure or ventricular dysfunction.[121] A total of 18,234 patients were studied in trials with at least 8 weeks of followup. The withdrawal rate was 24.3% in patients randomized to ACE inhibitors versus 27.8% in those allocated to reference treatment. Percentages of patients who withdrew due to worsening heart failure were 6.3% for ACE inhibitors and 11.7% in control groups (RR= 0.54; 95% CI 0.46-0.63). Excluding withdrawals due to MI and hypertension, withdrawals due to adverse events were 13.8% for ACE inhibitors and 9.4% for control groups (RR=1.54, 95% CI

1.30-1.83); for every 32 patients treated with an ACE inhibitor, one additional treatment withdrawal due to an adverse event occurred. Although adverse event rates for individual ACE inhibitors were not reported, there was no heterogeneity among the trials regarding withdrawals due to adverse events related to ACE inhibitors (p=0.14).

Observational studies. We identified no large, good-quality community-based or population-based observational studies designed to assess comparative safety of different ACE inhibitors. A large, fair-quality observational study conducted in multiple general practices in Germany[122] included 33,841 patients who were prescribed cilazapril. Patients were followed for an average of 109 days. At each check up patients were asked if they had experienced any adverse events. Adverse events were reported by 7.3% of patients during treatment, 6.7% of all patients discontinued treatment, and 3.8% of the study population discontinued due to adverse events. Forty-four patients died during the study (12 cardiac events, 10 cerebral events, 3 pneumonia, 2 accidents, 4 malignancies, 13 cause unknown). Dry cough was reported in 1.5% of all patients, and led to discontinuation of treatment in 1.1%.

Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one angiotensin converting enzyme inhibitor is more effective or associated with fewer adverse events?

No data suggest that one ACEI is better than others for demographic subgroups (age, race, gender). Although the recommended initial dose of trandolapril is higher in black than in non-black patients,[123] we found no data suggesting its efficacy is different from other ACEIs.

A 1995 meta-analysis of placebo-controlled trials of ACEIs in heart failure found no difference in total mortality or hospitalization in subgroups based on age, sex, NYHA Class, or etiology.[97] A more recent meta-analysis of the effectiveness of ACEIs in heart failure made 3 comparisons: blacks vs. whites, men vs. women, and diabetics vs. nondiabetics.[124] Its findings are summarized in Table 7.

Table 7. Results of meta-analysis by race, gender, and diabetes

Group of Interest	Number of Studies (Patients in group of interest)	RR for Mortality for Group of Interest (95% CI)	RR for Mortality for Other Subjects (95% CI)
Blacks	2 (800)	0.89 (0.74-1.06)	0.89 (0.82-0.97)
Women	6 (2,373)	0.92 (0.81-1.04)	0.82 (0.74-0.90)
Diabetics	6 (2,398)	0.84 (0.70-1.00)	0.85 (0.78-0.92)

Table from Shekelle, 2003[124]

In diabetics and in blacks, the effects of ACEIs were similar to those in the general population. However, women seemed to benefit less than men. The lack of effect in women was especially pronounced in studies that enrolled patients with *asymptomatic* LV dysfunction (RR Female 0.96, 95% CI 0.75-1.22; vs. for RR Female 0.90, 95% CI 0.78-1.05 for *symptomatic* HF). In men the effect was similar in patients with symptomatic and asymptomatic LV dysfunction.

ACEIs appear to have more beneficial effects in recent myocardial infarction patients at higher risk for recurrent cardiovascular events (patients with heart failure, diabetes, or hypertension), but no single ACEI has been found to be superior for any of these conditions.[69, 75, 125-131]

Patients with renal insufficiency or renal disease. Trials in patients with recent MI generally excluded patients with renal disease. There are no data from head-to-head trials about the comparative efficacy of different ACEIs in patients with recent myocardial infarction and renal insufficiency.

Similarly, there is little information about ACEIs in patients with heart failure and renal insufficiency. Most trials either excluded patients with renal disease, or did not perform a subgroup analysis of patients with renal insufficiency.[132] CONSENSUS, a placebo-controlled trial of enalapril in patients with severe heart failure, included patients with moderate renal insufficiency (median serum creatinine level 1.4 mg/dL). Overall, patients in the enalapril group had 31% lower mortality at 1 year, and those with baseline serum creatinine levels greater than and less than the median had similar survival benefit.[56] There are no data from head-to-head trials about the comparative efficacy of different ACEIs in patients with heart failure and renal insufficiency.

Blacks. At present, the role of ACEIs in the management of hypertension, recent myocardial infarction, and heart failure, and patients with kidney disease is the same for blacks and nonblacks. There are no head-to-head trials comparing one ACEI to another in black patients.

One trial enrolled only black patients. The AASK trial (see Table 3, above) compared an ACEI, a beta blocker, and a calcium channel blocker in black patients with hypertensive kidney damage. The primary outcome measure was reduction in GFR by 50% or more (or > or =25 mL/min per 1.73 m2) from baseline, ESRD, or death. Compared with the metoprolol and amlodipine groups, the ramipril group manifested risk reductions in this clinical composite outcome measure of 22% (95% CI, 1%-38%; p=.04) and 38% (95% CI, 14%-56%; p=.004), respectively.[11]

AASK did not include a diuretic as one of the treatments. In ALLHAT, which enrolled hypertensive patients who did not have the advanced kidney damage of the AASK patients, a diuretic was better than an ACEI (lisinopril) for preventing cardiovascular events in all races.[12]

This was especially true for blacks: rates of stroke were 40% higher in the lisinopril group versus chlorthalidone in blacks, with no difference in non-blacks; rates of combined CVD endpoint were 19 % higher in blacks compared to a 6 percent increased rate in non-blacks.

Black patients who take ACEIs are at higher risk of developing angioedema, a complication of ACEI therapy, than other Americans. The risk is two[12] to four times[133] as high in African-Americans ACEI users as in other American users. In the AASK trial, the rates of angioedema over 3.5 to 6 years of followup were 6.4% for ramipril, versus 2.3% and 2.7% for the other drugs ($p<0.05$ for both comparisons). In ALLHAT, rates of angioedema were higher in blacks than non-blacks (0.7% vs 0.3%) and higher in lisinopril compared to Chlorthalidone in both blacks and non-blacks. There is currently no evidence that one ACEI is safer than others for black patients.

Elderly. One fair quality head-to-head trial of lisinopril 5 mg to 20 mg once daily versus captopril 12.5 mg to 50 mg three times daily analyzed a subgroup of 65 patients over age 65.[84] There was no difference between treatment groups in change in NYHA class after 12 weeks of treatment. Increase in exercise duration was slightly, but not significantly, higher in the captopril group (134.3 vs 71.8 seconds, $p=0.08$). A second fair-quality trial[87] of lisinopril versus captopril in patients ages 65 to 80 also found no difference in change in NYHA class after 12 weeks.

Other drugs. ACEIs appear to be effective when used with nitrates,[67, 68] aspirin,[134] thrombolytics,[61] and other agents conventionally used to treat myocardial infarction, but there are no data regarding comparative efficacy or safety in patients on these medications. Many trials excluded patients with severe hypotension or renal failure, and we found no data to suggest that one ACEI is superior to others for patients with these conditions. Theoretically, an ACEI with a shorter half-life (captopril) may be safer in patients at risk for severe hypotension or acute renal failure, but we found no trials comparing the safety of captopril versus longer-acting ACEIs in these patients.

SUMMARY

Tables 8 and 9 summarize the results of this review. There is evidence from head-to-head trials that, especially in heart failure, many ACEIs are similar in short-term effectiveness and adverse events. Several ACEIs reduce mortality after MI in various subgroups (no HF, asymptomatic LV dysfunction, and clinical HF). There is no definitive evidence that they differ in long-term effectiveness for major cardiovascular and renal endpoints. Across indications, the evidence for mortality reductions is strongest for captopril, enalapril, and ramipril.

Table 8. Outcomes data for ACEIs

Drug	Hypertension without compelling indications	Hypertension plus Diabetes	Known Coronary Disease	Recent myocardial infarction	Heart Failure	Diabetic Nephropathy	Other nephropathy
Benazepril					Reduced mortality and hospitalization in 2 small placebo-controlled studies.	Reduced ESRD/death in patients with renal disease, 21% had diabetes.	
Captopril	=diuretic, beta blocker	= beta blocker		Consistently reduced mortality and heart failure in several trials	Improved functional outcomes in head-to-head trials. Reduced mortality in placebo-controlled studies.	Reduced ESRD/death and onset of hypertension in Type I diabetics	
					Cilazapril		
Enalapril	> diuretic	> CCB	Reduced major CV events	>captopril in a small head-to-head trial, but placebo-controlled studies had inconsistent results	Improved functional outcomes in head-to-head trials. Reduced mortality in placebo-controlled studies.		
Fosinopril		> CCB		1 small trial, reduced heart failure but no mortality benefit	vs. enalapril, NS trend toward lower mortality. Improved functional outcomes in head-to-head trials.		

Lisinopril	=diuretic	=diuretic		reduced mortality at 6 months in a large, good-quality trial	Improved functional outcomes in head-to-head trials. Reduced mortality and hospitalization in 3 small placebo-controlled studies.	
Moexipril						
Perindopril			Reduced CV events but no difference in overall mortality in 1 large placebo controlled trial. No difference from placebo in 1 trial	= captopril for mortality and revascularization rates in one small head-to-head trial	Non-significant reduction in mortality in one small placebo-controlled trial.	
Quinapril			No difference from placebo in one trial. Reduced risk of composite of MI, stroke, all-cause mortality in one post-revascularization study		Improved functional outcomes in head-to-head trials. Reduced mortality in placebo-controlled studies.	
Ramipril			Reduced all-cause mortality and major CV events in 2 studies; non-significant trend toward benefit in another study.	Reduced mortality and heart failure in a large, good-quality trial	Improved functional outcomes in head-to-head trials. Reduced mortality in placebo-controlled studies.	Reduced ESRD/death in blacks with hypertensive renal disease and in nondiabetics with renal disease.
Trandolapri l				Reduced mortality and heart falure in a large, good-quality trial	Reduced mortality in a large, good-quality trial	

CCB= calcium channel blocker, ESRD=end-stage renal disease or doubling of creatinine.

Table 9. Summary of evidence comparing ACE inhibitors to one another

Comparative efficacy	Overall Grade of Evidence**	Conclusion
Key question 1:		
a. Hypertension	Good for quality of life	Long-term quality of life was better with captopril than with enalapril.
	Fair for cardiovascular outcomes	
	Poor for other long-term health outcomes	No other outcomes assessed in head-to-head trials
b. High cardiovascular risk factors	Fair	There are no head-to-head trials. In patients who have a history of coronary disease with or without hypertension, and other patients at high risk of CAD, ramipril is the only ACEI to reduce all-cause mortality (NNT 56). Enalapril, perindopril, and ramipril reduced major cardiovascular events in patients with CAD.
c. Recent myocardial infarction	Fair	1 fair-quality head-to-head trial (Foy 1994) of captopril vs. enalapril found a significant difference in mortality (12% vs. 1%) but this was a relatively small trial (n=225). Another fair-quality head-to-head trial (Lau 2002) found no significant differences for mortality or revascularization rates for captopril vs. perindopril. No other head-to-head trials of included ACE-I's was available. Captopril, lisinopril (6-months), ramipril, and trandolapril reduced mortality and heart failure in good-quality, placebo-controlled trials. Enalapril had a slight trend towards increased mortality in a large, good-quality placebo-controlled trial, but significantly reduced the rate of heart failure requiring hospitalization. In a smaller placebo-controlled trial, there was a trend towards increased mortality and decreased heart failure on fosinopril.

Table 9. Summary of evidence

Comparative efficacy	Overall Grade of Evidence**	Conclusion
Key question 1 (continued):		
d. Heart failure	Good for functional outcomes Fair for mortality and major CV events.	1 fair-quality head-to-head trial showed no difference in total mortality between fosinopril vs enalapril. Decreased hospitalization plus mortality in fosinopril group may have been due to dosing schedule. 1 fair-quality meta-analysis of 32 placebo controlled trials showed no heterogeneity of effect for mortality or mortality plus hospitalization among benazepril, captopril, cilazapril, enalapril, lisinopril, perindopril, quinapril, and ramipril, with most evidence from trials of captopril, enalapril, ramipril, quinapril, and lisinopril, and limited evidence for benazepril (2 studies), cilazapril (1 study), and perindopril (1 study) was limited, In 15 head-to-head trials there was no difference in improvement in NYHA class or exercise duration for captopril, enalapril, fosinopril, lisinopril, quinapril, and ramipril. There are no head-to-head trials of benazepril, trandolapril, moexipril, or perindopril, and no placebo-controlled trials of moexipril.
e. Diabetic and nondiabetic nephropathy	Poor	There are no head-to-head trials. Captopril reduced ESRD and death, but only in patients with longstanding Type 1 diabetes. Several ACEIs reduce proteinuria in diabetics. Benazepril reduced end-stage renal disease and doubling of creatinine in one placebo controlled trial of patients with renal insufficiency from various causes and no hypertension. Effect was stronger in the subgroup with diabetic nephropathy.
Key question 2:		
General	Poor	There is no evidence that any ACEI is associated with a lower risk of serious complications than other ACEIs.
For specific indications		
Recent myocardial infarction	Fair/Poor	Adverse event assessment quality was generally worse than quality for assessing clinical efficacy. 2 head-to-head trials provided inconclusive evidence regarding comparative efficacy. Placebo-controlled trials provided no additional data.
Heart failure	Fair	No good or fair quality head-to-head trial was designed to assess safety. Withdrawals due to adverse effects did not differ in 9 head-to-head trials. A meta-analysis of 51 placebo-controlled trials found no heterogeneity of effect among ACE inhibitors. There are no head-to-head trials of benazepril, trandolapril, moexipril, or perindopril, and no placebo-controlled trials of fosinopril, moexipril, or trandolapril.

Table 9. Summary of evidence

Comparative efficacy	Overall Grade of Evidence**	Conclusion
Key question 3:		
Women	Poor	For heart failure, ACEIs may be less effective in women. There are no data on how different ACEIs compare in women.
Blacks	Fair	ACEIs are as effective in blacks as in whites. There are no data on how different ACEIs compare in blacks.
Elderly patients	Fair	In 2 fair quality trials of lisinopril vs captopril for heart failure in elderly patients, there was no evidence that one was more effective than another. A meta-analysis of 32 trials found no differences among ACEIs based on age.

Quality of evidence ratings **for distinguishing among ACEIs based on criteria developed by the US Preventive Services Task Force.

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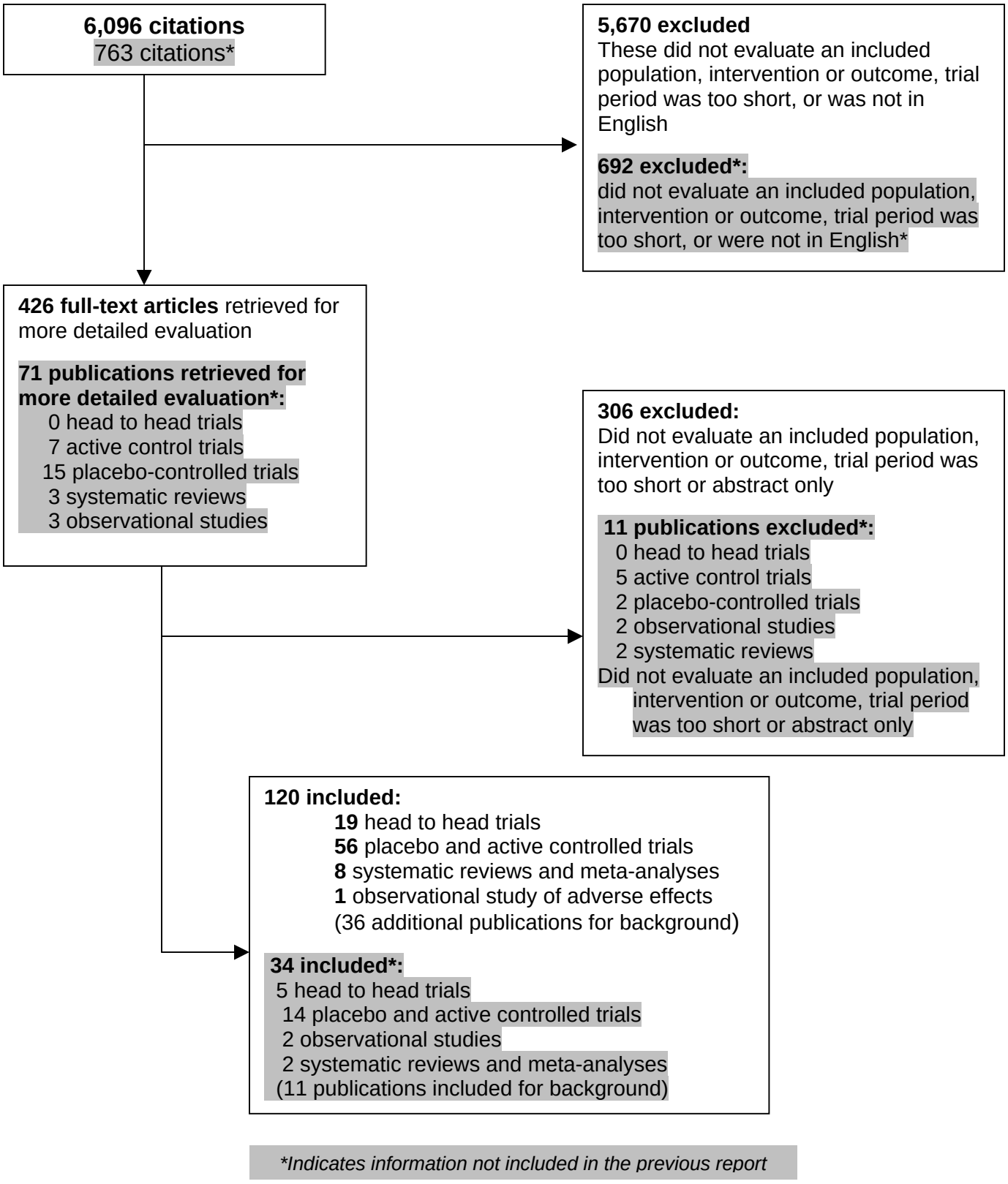
Figure 1: ACE Inhibitors drug class review flow diagram



Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/Washout
PEACE Trial Investigators, 2004 Multiple centers in the US (including Puerto Rico), Canada, and Italy (GOOD)	1) Age 50 years or older; 2) coronary disease documented by at least one of the following: myocardial infarction at least 3 months before enrollment, CABG or percutaneous transluminal coronary angioplasty at least 3 months before enrollment,obstruction of 50% or more of the luminal diameter of at least one native vessel on coronary angiography; 3) Left ventricular ejection fraction >40% on contrast or radionuclide ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of left ventricular wall-motion abnormalities on echocardiography; 4) toleration of the medication and successful completion of the run-in phase, with 80% or greater compliance with the medication.	trandolapril 2 mg; raised to 4 mg after 6 months if 2 mg dose tolerated.	2-week run-in during which patients were asked to take trandolapril 2 mg per day; excluded if compliance was poor or if they had side effects or an abnormal rise in serum creatinine or potassium.
Otsuka et al, 2004 Japan (FAIR)	Patients with coronary artery disease who had been successfully treated with PCI. Procedural success was defined as an immediate percent diameter stenosis <50%.	Quinapril 10 mg to 20 mg	None

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
PEACE Trial Investigators, 2004 Multiple centers in the US (including Puerto Rico), Canada, and Italy (GOOD)	Angiotensin II-receptor antagonists not allowed. Allowed calcium channel blocker (36%), beta blocker (60%), aspirin or antiplatelet medication (90%), lipid-lowering drugs (70%), diuretic agent (13%) digitalis (4%), antiarrhythmic agents (2%), anticoagulants (5%), insulin (4%).	Primary endpoint: death from cardiovascular causes or nonfatal MI. Secondary endpoint: composite of death from cardiovascular causes, nonfatal MI, or coronary revascularization. A morbidity and mortality review committee reviewed and classified all outcomes.	Mean age 64±8 19% trandolapril vs 17% placebo female (p<0.05) 93% white	History of: MI: 55% Coronary disease on angiography: 61% Angina pectoris: 71% Percutaneous coronary intervention: 41% CABG: 39% PCI or CABG: 72% Diabetes: 17% Hypertension: 46% Diabetes with history of hypertension or dbp ≥90mmHg or SBP ≥140mmHg Stroke or transient ischemic attack: 7% Current cigarette smoking: 14%
Otsuka et al, 2004 Japan (FAIR)	Aspirin (81-250 mg per day, indefinitely) and ticlopidine (if treated with stents, 200 mg twice per day for 4 weeks) administered as adjunct pharmacologic therapy. After randomization, 62% treated with calcium channel blockers, 9% with beta blockers, 75% with nitrates, and 30% with statins.	Clinical information obtained at the outpatient clinic, by telephone interview, or via the referring physician. Major clinical endpoints included death (regardless of cause), MI (occurrence of typical symptoms, EKG changes and serum creatine kinase elevations to twice the upper normal limit), cerebrovascular accident, or revascularization. When >1 clinical endpoint occurred in a patient, only the first event was counted for the survival analysis.	Mean age 63 years 72% male 100% Asian	46% treated for hypertension, 33% diabetes, 53% hypercholesterolemia, 36% acute MI, mean ejection fraction 64%.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
PEACE Trial Investigators, 2004 Multiple centers in the US (including Puerto Rico), Canada, and Italy (GOOD)	# screened not reported/# eligible not reported/8290 enrolled after run-in	11 withdrawn/134 lost to followup/8290 analyzed	**Trandolapril vs placebo**: Primary endpoint: 21.9% vs 22.5% Hazard ratio 0.96 (0.88-1.06; p=0.43) Death from CV causes: 3.5% vs 3.7%; Hazard ratio 0.95 (0.76-1.19; p=0.67) Nonfatal MI: 5.3% vs 5.3%; Hazard ratio 1.00 (0.83-1.20; p=1.00) CABG: 6.5% vs 7.1% Hazard ratio 0.91 (0.77-1.07; p=0.24) PCI: 12.4% vs 12.0% Hazard ratio 1.03 (0.91-1.16; p=0.65) Death from non-CV or unknown causes: 3.7% vs 4.4% Hazard ratio 0.83 (0.67-1.03; p=0.09) Death from any cause: 7.2% vs 8.1% Hazard ratio 0.89 (0.76-1.04; p=0.13)
Otsuka et al, 2004 Japan (FAIR)	# screened, eligible not reported/253 enrolled	Of quinapril patients, 58% still taking quinapril at 1 year, 46% at 2 years, 40% at 3 years, and 31% at final followup/0 lost to followup/253 analyzed	**Quinapril vs control (no placebo)** *%; relative risk (95% CI)* : Death at 6 months: 0% vs 0.8% Death at 4 years: 3.8% vs 9.8%; 0.40 (0.14-1.13) MI at 6 months: 0.7% vs 2.5% MI at 4 years: 2.3% vs 4.1%; 0.56 (0.13-2.33) CVA at 6 months: 0% vs 0% CVA at 4 years: 2.3% vs 3.3%; 0.71 (0.16-3.19) Revascularization at 6 months: 23.7% vs 35.2%; 0.57 (0.33-0.99) Revascularization at 4 years: 26.0% vs 37.7%; 0.62 (0.40-0.97) Any event at 6 months: 24.4% vs 36.1%; 0.57 (0.33-0.99) Any event at 4 years: 29.8% vs 46.7%; 0.58 (0.38-0.86)

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals/withdrawals due to adverse events
PEACE Trial Investigators, 2004 Multiple centers in the US (including Puerto Rico), Canada, and Italy (GOOD)	NR	trandolapril vs placebo: cough: 39.1% vs 27.5% (p<0.01) syncope: 4.8% vs 3.9% (p=0.04) angioedema: 5/4132 (0.1%) vs 8/4158 (0.2%; 2 receiving open-label ACEI)	Total withdrawals: 3/4158 trandolapril (0.07%), 8/4132 placebo (0.2%) Withdrawals due to AEs: 14.4% trandolapril, 6.5% placebo (p<0.001)
Otsuka et al, 2004 Japan (FAIR)	NR	NR	Total withdrawals: NR Withdrawals due to AEs: cough 20%, hypotension 7%, renal dysfunction 2% (groups not reported)

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/Washout
Nissen et al, 2004 Multicenter, US, Canada, and Europe CAMELOT Study (FAIR)	Men and women ages 30 to 79 years, requiring coronary angiography for evaluation for chest pain or PCI; DBP lower than 100 mgHg, with or without treatment.	enalapril 10 mg, raised to 20 mg after 1 week.	2-week placebo run-in. Patients demonstrating at least 80% compliance were randomized. ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers were discontinued over a 2- to 6-week period.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Nissen et al, 2004 Multicenter, US, Canada, and Europe CAMELOT Study (FAIR)	Angiotensin receptor blockers and calcium channel blockers prohibited; beta blockers, alpha-1 blockers, and diuretics were permitted.	Primary outcome: incidence of adverse cardiovascular events in patients treated with amlodipine compared with placebo. Events included in the endpoint were cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and any new diagnosis ofperipheral vascular disease. Secondary outcomes included all-cause mortality and revascularization.	Mean age 57 (± 10) 72% male	History: 60% hypertension, 4% stroke, 18% diabetes, 8% Class 4 angina (angina at any level of exertion), 28% PCI, 8% CABG, 38% MI, 26% current smoker

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Nissen et al, 2004 Multicenter, US, Canada, and Europe CAMELOT Study (FAIR)	# screened, eligible not reported/1332 enrolled (excluding amlodipine)	4 withdrawn/38 lost to followup/1328 analyzed (excluding amlodipine)	**Enalapril vs placebo**: *Event rates (%), Hazard ratio (95% CI); p-value* Primary endpoint: 20.2% vs 23.1%; 0.85 (0.67-1.07); p=0.16 Coronary revascularization: 14.1% vs 15.7%; 0.86 (0.65-1.14); p=0.30 Hospitalization for angina: 12.8% vs 12.8%; 0.98 (0.72-1.32); p=0.87 Nonfatal MI: 1.6% vs 2.9%; 0.55 (0.26-1.15); p=0.11 Stroke or TIA: 1.2% vs 1.8%; 0.66 (0.27-1.62); p=0.36 Cardiovascular death: 0.7% vs 0.3%; 2.33 (0.45-12.1); p=0.16 Hospitalization for CHF: 0.6% vs 0.8%; 0.78 (0.21-2.90); p=0.71 Resuscitated cardiac arrest: 0.1% vs 0.6%; 0.24 (0.03-2.15); p=0.17 New-onset peripheral vascular disease: 1.2% vs 0.3%; 3.91 (0.83-18.4); p=0.06 Revascularization after baseline PCI: 6.2% vs 7.9%; 0.75 (0.50-1.13); p=0.17 All-cause mortality: 1.2% vs 0.9%; 1.26 (0.44-3.65); p=0.67

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals/withdrawals due to adverse events
Nissen et al, 2004 Multicenter, US, Canada, and Europe CAMELOT Study (FAIR)	NR	enalapril vs placebo: hypotension: 905% vs 3.2% Peripheral edema: 9.5% vs 9.6%	Total withdrawals: 35.1% enalapril, 31.1% placebo (NS) Withdrawals due to AEs: 13% overall Enalapril discontinued for cough in 3.9% of patients.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/Washout
Kjoller-Hansen et al, 2000, Kjoller-Hansen et al, 2004 Single center, Denmark APRES (FAIR)	Patients undergoing coronary angiography, ages 18 to 75 years, no prior cardiac surgery, LVEF between 0.30 and 0.50 and referred for invasive revascularization with CABG or PTCA for angina pectoris after coronary angiography and clinical evaluation.	ramipril 5 mg	Test dose of ramipril 2.5 mg given; if tolerated, randomized to 5 mg or placebo; increased to 10 mg after one month if tolerated.
EUROPA Investigators, 2003 Multiple European countries EUROPA Study (FAIR)	At least 18 years old without clinical evidence of heart failure and with evidence of coronary heart disease, documented by previous MI (>3 months prior), percutaneous or surgical coronary revascularization (>6 months prior), or angiographic evidence of at least 70% narrowing of one or more major coronary arteries. Men could also be recruited if they had a history of chest pain and a positive EKG, echo, or nuclear stress test.	Perindopril 8 mg. Reduced to 4 mg if not tolerated.	4 week run-in: patients received 4 mg perindopril once daily for 2 weeks in addition to their normal medicaiton, followed by 8 mg perindopril for 2 weeks if the lower dose was well tolerated. Patients aged 70 or older were given 2 mg perindopril in the first week, followed by 4 mg in the second week, and 8 mg in the last 2 weeks. Excluded from randomization if hypotension, raised potassium or creatinine concentratins, other intolerance, major clinical events, poor adherence to treatment, exclusion or non-inclusion criteria, withrawn consent, unspecified stop reason, and patients never randomized.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Kjoller-Hansen et al, 2000, Kjoller-Hansen et al, 2004 Single center, Denmark APRES (FAIR)	Other cardiac drugs (% taking at baseline) beta blockers (30%); calcium antagonists (10%); diuretics (21%); aspirin (100%); statins (30%)	Primary endpoint: composite of cardiac death, nonfatal acute MI, development of heart failure or recurrent angina pectoris. Followup visits scheduled at one, three, and six months after randomization and every 6 months thereafter. Median followup of 2.5 years was intended with a minimum followup of one year.	Mean age 61 89% male ethnicity not reported.	27% hypertension, 9% diabetes, 86% smoker (parst or current); mean duration of angina 3.6 years, 77% acute MI by history, mean interval since last MI 2.7 years.
EUROPA Investigators, 2003 Multiple European countries EUROPA Study (FAIR)	Yes (lipid lowering drugs, beta blockers, calcium channel blockers)	Primary endpoint: composite of cardiovascular death, non-fatal MI, and cardiac arrest with successful resuscitation. Initially, the primary endpoint was defined as the composite of total mortality, non-fatal MI, unstable angina, and cardiac arrest with successful resuscitation. Primary endpoint was changed towards the end of the initial proposed followup period. Mean 4.2 years followup. Followup was originally to be 3 years. At the end of 3 years, the definition of primary endpoint was changed and study was extended by one year.	Mean age 60 years (SD 9) 85% male ethnicity not reported	65% previous MI, 55% previous revascularization, 12% diabetes, 27% hypertension, 63% hypercholesterolemia.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Kjoller-Hansen et al, 2000, Kjoller-Hansen et al, 2004 Single center, Denmark APRES (FAIR)	Nearly 3000 screened/213 eligible/159 enrolled	NR/NR/159 analyzed	**Ramipril vs placebo**: *incidence (%), % risk reduction (95% CI), NNT, p-value* Cardiac death, AMI, clinical heart failure, or recurrent angina: 45% vs 52%; Risk Reduction (RR)=10% (-41%, 43%); p=0.63 Cardiac death, AMI, or clinical heart failure: 10% vs 23%; RR=58% (7%, 80%); NNT=8; p=0.031 Cardiac death or AMI: 2.5% vs 11.4%; RR=78% (12%, 92%); NNT=11; p=0.034 Cardiac death or clinical heart failure: 8.8% vs 21.5%; RR=61% (7%, 80%); NNT=8; p=0.024 Cardiac death: 1.3% vs 8.9%; RR=86% (14%, 95%); NNT=13; p=0.032 AMI: 1.3% vs 5.1%; p=0.21 Clinical heart failure: 7.5% vs 15.2%; RR=40% (-18%, 82%); p=0.10 Recurrent angina: 42.5% vs 40%; RR= -19% (-90%, -37%); p=0.23
EUROPA Investigators, 2003 Multiple European countries EUROPA Study (FAIR)	# screened not reported/13,655 eligible/12,218 enrolled after run-in	2657 withdrawn/3 lost to followup/12,215 analyzed	CV events (cardiovascular death, non-fatal MI, cardiac arrest with successful resuscitation) at (mean followup) 4.2 years NNT=50 RR 0.80 (0.71-0.91) All-cause mortality at 4.2 years RR=0.89 (0.77-1.02)

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals/withdrawals due to adverse events
Kjoller-Hansen et al, 2000, Kjoller-Hansen et al, 2004 Single center, Denmark APRES (FAIR)	Occurrences of adverse events were recored at visits at one, three, and six months after randomization and every six months thereafter. Patients were instructed to contact the study physicians between scheduled visits in case of health-related problems.	38% ramipril, 34% placebo experienced minor adverse evnets, the most frequent being tiredness, GI disturbances, dizziness, and cough. A tnedency towards a higher frequency of coughing, tiredness ,a nd dizziness in the ramipril group was found (data not reported).	Total withdrawals: 13/80 (16%) ramipril, 13/79 (16%) placebo. Withdrawals due to AEs: 3% ramiipril, 3%, 4% placebo.
EUROPA Investigators, 2003 Multiple European countries EUROPA Study (FAIR)	Not reported	"specific adverse effects, such as cough, hypotension, or abnormal creatinine rise were infrequent."	Total withdrawals not reported ('withdrawals from treatment were similar to those for placebo'); withdrawals for cough 2.7% perindopril vs 0.5% placebo.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/Washout
HOPE Study Investigators, 2000 Mann 2003 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial 2 X 2 factorial design (vitamin E and ramipril) Multicenter (FAIR)	At least 55 years old with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol, low HDL-C, cigarette smoking, or documented microalbuminuria.	Ramipril 10 mg	In run-in, all patients received 2.5 mg ramipril for 7 to 10 days followed by matching placebo for 10 to 14 days. Excluded from randomization for noncompliance, side effects, abnormal serum creatinine or potassium levels, or withdrawal of consent.
Marre et al. 2004 Multiple European countries DIABHYCAR Study (GOOD)	Over age 50 with type 2 diabetes (defined on the basis of receiving current treatment with at least one oral antidiabetic agent), urinary albumin excretion 20 mg/l or higher in 2 successive random urine samples.	Ramipril 1.25 mg once daily.	Not reported
MacMahon, 2000 Australia and New Zealand PART2 Trial (FAIR)	Age 75 or younger with a hospital diagnosis (within 5 years of enrollment) of any of the following: acute MI, angina with coronary disease confirmed by angiograpy or exercise EKG, transient ischemic attack or intermittent claudication.	Ramipril 5-10 mg	2-week run-in in which patients received ramipril 5 mg daily for the first week and ramipril 10 mg daily for the second week. Compliant patietns who tolerated at least 5 mg ramipril daily were randomized.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
HOPE Study Investigators, 2000 Mann 2003 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial 2 X 2 factorial design (vitamin E and ramipril) Multicenter (FAIR)	All patients received vitamin E or placebo vitamin E. Other medications not reported.	Primary outcome: composite of myocardial infarction, stroke, or death from cardiovascular causes. Followup 5 years. Secondary outcome: Development of renal disease over 4.5 years (n=7674)	Mean age 66 years (SD 7) 73.3% male ethnicity not reported	History of CVD (80%) or diabetes (38%) plus one other risk factor (HTN—47%, High cholesterol—66%, smoking—14%). Patients with nephropathy or heart failure were excluded.
Marre et al. 2004 Multiple European countries DIABHYCAR Study (GOOD)	Usual treatment; ~47.5% were using antihypertensive agents, ~ 28% lipid lowering agents, ~18.5% antiplatelets.	Primary endpoint: combined incidence of cardiovascular death (including sudden death), non-fatal acute MI, stroke, heart failure requiring admission to hospital, and end stage renal failure (defined as requirement for hemodialysis or kidney transplant). Investigators examined participants every six months for at least 3 years.	Mean age 65 (SD 8) 70% male ethnicity not reported	56% hypertensive ((>140/90 mm Hg and taking antihypertensive drugs), 73%-74% microalbuminuria, 26% proteinuria, 77.6% ramipril and 73.6% placebo had no previous cardiovascular disease
MacMahon, 2000 Australia and New Zealand PART2 Trial (FAIR)	Not reported	Primary outcome measures were ultrasound recordings of the carotid arteries and echocardiograms. Details of all clinical events resulting in death, hospitalization, or withdrawal from study treatment were also recorded throughout followup. Followup 4 years.	Mean age 61 82% male Ethnicity not given	Medical history (ramipril vs placebo): MI 43% vs 41% Angina 66% vs 65% Peripheral vascular disease 20% vs 20% TIA or stroke 11% vs 9% Type I diabetes 2% vs 3% Type II diabetes 6% vs 6%

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
HOPE Study Investigators, 2000 Mann 2003 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial 2 X 2 factorial design (vitamin E and ramipril) Multicenter (FAIR)	# screened not reported/#eligible not reported/9,297 enrolled	# withdrawn not reported/# lost to followup not reported/9,297 analyzed	**CV events at 5 years:** NNT 26.7 RR 0.79 (0.72-0.86) **All-cause mortality at 5 years:** NNT 56 RR 0.84 (0.75-0.95) Development of Renal Disease at 4.5 years:
Marre et al. 2004 Multiple European countries DIABHYCAR Study (GOOD)	25,468 screened/5,948 eligible/4,937enrolled	678 dropped out/160 lost to followup/4912 analyzed (25 withdrawn due to major misconduct by investigator were withdrawn after randomization)	Primary end point (combined) at 3-6 (median 4) years of followup: ramipril 362/2443 (14.8%) vs placebo 377/2469 (15.3%) RR 0.97 (95% CI 0.85 to 1.11) p=0.66 *Also no significant differences on individual components of primary endpoints or on secondary enpoints.*
MacMahon, 2000 Australia and New Zealand PART2 Trial (FAIR)	# screened not reported/744 eligible/617 enrolled after run-in	Not reported	**CV events** NNT 44.8 RR 0.83 (0.54-1.28) **All-cause mortality** RR 0.64 (0.35-1.18)

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals/withdrawals due to adverse events
HOPE Study Investigators, 2000 Mann 2003 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial 2 X 2 factorial design (vitamin E and ramipril) Multicenter (FAIR)	"Serious adverse events are recorded."	cough, hypotension or dizziness, angioedema were reasons for withdrawal.	ramipril vs placebo: 28.9% vs 27.3% withdrew overall 7.3% vs 1.8% withdrew due to cough 1.9% vs 1.5% withdrew due to hypotension or dizziness 0.4% vs 0.2% withdrew due to angioedema.
Marre et al. 2004 Multiple European countries DIABHYCAR Study (GOOD)	Not reported	1 ramipril and 1 placebo patient developed angioedema; 6.3% ramipril and 4.0% placebo reported non-serious adverse events (cough most frequent); 43.2% ramipril vs 44.4% placebo reported serious adverse events (most frequent inadequate control of diabetes).	14% of ramipril vs 13.5% placebo withdrew 3.3% ramipril vs 0.9% placebo withdrew due to coughing.
MacMahon, 2000 Australia and New Zealand PART2 Trial (FAIR)	Not reported	Not reported	Not reported

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/Washout
Pitt, 2001 US, Canada, Europe QUIET Study (FAIR)	18 to 75 years of age, had undergone successful coronary angioplasty or atherectomy at baseline, and had at least 1 coronary that had not been subjected to mechanical revascularization.	Quinapril 20 mg	None
Teo, 2000 Canada SCAT Trial 2 X 2 factorial design (simvastatin and enalapril) Multicenter (FAIR)	Age 21 or older, total serum cholesterol 4.1-6.2 mmol/L, HDL cholesterol <2.2 mmol/L and triglycerides <4 mmol.L and lower than total cholesterol, angiographically detectable coronary atherosclerosis in 3 or more major coronary arter segments, and left ventricular ejection fraction >35%. Patients not enrolled within 6 months of coronary angioplasty or bypass surgery.	Enalapril 5-20 mg	1-month, single-blind, placebo run-in. Criteria for withdrawal after run-in not reported.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Pitt, 2001 US, Canada, Europe QUIET Study (FAIR)	Excluded calcium channel blockers and lipid-lowering agents; subset of 453 randomly selected patients underwent repeat coronary angioplasty.	Occurrence of 1 of the following cardiac events: cardiac death, resuscitated cardiac arrest, nonfatal MI, coronary artery bypass graft surgery, coronary angioplasty, or hospitalization for angina pectoris. Primary outcome was time to first cardiac event. Followup 2 years	Mean age 58 years 82% male 94% white	History of PTCA, normal lipid levels
Teo, 2000 Canada SCAT Trial 2 X 2 factorial design (simvastatin and enalapril) Multicenter (FAIR)	2 X 2 factorial design included simvastatin; all patients instructed to follow cholesterol-lowering diet.	Study endpoints were Quantitative coronary angiography measures and prespecified clinical events (death, MI, stroke, hospitalization for angina, revascularization, and cancer). Clinical endpoints were not powered to detect conclusive differences. Followup 4 years	Mean age 61 (SD 9) 89% male Ethnicity not reported	History: 54% angina; 70% MI, 11% diabetes, 36% hypertension, 15% current smoker, 67% previous smoker.

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Results
Pitt, 2001 US, Canada, Europe QUIET Study (FAIR)	# screened not reported/# eligible not reported/1,750 enrolled	464 withdrew/4 lost to followup/1,750 analyzed	**CV events** NNT 139 RR 0.88 (0.61-1.29) *Too small to assess all-cause mortality.*
Teo, 2000 Canada SCAT Trial 2 X 2 factorial design (simvastatin and enalapril) Multicenter (FAIR)	>16,500 charts and 4,000 coronary angiograms screened/number eligible not reported: "one third of patients entering run-in were not randomized"/460 enrolled/	Not reported for clinical endpoints.	**CV events** NNT 16 RR 0.47 (0.24-0.90) *Too small to assess all-cause mortality.*

Evidence Table 1. Placebo-controlled trials of ACE Inhibitors in patients with known or likely coronary disease

Author Year Setting (Quality Rating)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals/withdrawals due to adverse events
Pitt, 2001 US, Canada, Europe QUIET Study (FAIR)	Not reported	Not reported	"Frequency and reasons for withdrawal in placebo and quinapril were similar. Cough was the only treatment-associated adverse event leading to a significantly higher percentage of withdrawals in the quinapril than placebo group." (3.8% vs 0.2%)
Teo, 2000 Canada SCAT Trial 2 X 2 factorial design (simvastatin and enalapril) Multicenter (FAIR)	Monitored (serum biochemical monitoring)	No differences in frequency of elevated serum potassium and creatinine levels between groups.	Not reported

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
EUROPA Investigators, 2003; Gomma 2001 Multiple countries in Eastern and Western Europe EUROPA Study	Method not reported	Method not reported	Yes	Yes	Yes	Not reported	Yes
HOPE Study Investigators, 2000, 1996 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial	Yes	Method not reported	Yes	Yes	Yes	Not reported	Yes
Marre et al. 2004 Multiple European countries DIABHYCAR Study (GOOD)	Yes	Method not reported	Yes	Yes	Yes	Not reported	Yes

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating	Number screened/ eligible/ enrolled
EUROPA Investigators, 2003; Gomma 2001 Multiple countries in Eastern and Western Europe EUROPA Study	Attrition and adherence yes; crossovers and contamination no	No	Yes, able to calculate; endpoints on all but 3 patients (all perindopril)	No	Fair	Number screened not reported/ 13,655 eligible/ 12,216 enrolled
HOPE Study Investigators, 2000, 1996 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial	attrition yes; crossovers no; adherence yes; contamination yes (reports # of placebo patients receiving an ACE inhibitor, but % specifically ramipril not reported)	No	Yes	No	Fair	Number screened not reported/ 10,576 eligible/ 9,297 enrolled
Marre et al. 2004 Multiple European countries DIABHYCAR Study (GOOD)	Yes	No	Yes, able to calculate (25/4937 not analyzed)	Yes- 25 patients at 20 centers withdrawn due to misconduct by investigator	Fair	25,468 screened/5948 eligible/4937 enrolled

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Exclusion criteria	Run-in/ Washout?	Class-naive patients?
EUROPA Investigators, 2003; Gomma 2001 Multiple countries in Eastern and Western Europe EUROPA Study	Clinical evidence of heart failure, planned revascularization, hypotension (SBP <110 mm Hg), uncontrolled hypertension (SBP >180 ,, Hg, DBP >100 mm Hg, or both), recent (<1 month) use of ACE inhibitors or angiotensin-receptor blockers, renal insufficency (creatinine >150 mol/L), and serum ppotassium higher than 5.5 mmol/L.	Run-in	No
HOPE Study Investigators, 2000, 1996 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial	Current use of an ACE inhibitor or vitamin E and inability to discontinue these; known hypersensitivity to an ACE inhibitor or vitamin E; ejectio fraction <40%; hemodynamically significant primary valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes presumed to be due to uncontrolled life-threating arrhythmias, planned cardiac surgery or angioplasty within 3 months, uncontrolled hypertension, cor pulmonale, heart transplant recipient; signicicant renal disease, any other major noncardiac illness expected to reduce life expectancy or interfere with study participation; simultaneously taking anohter experimental drug, previously randomized by HOPE.	Run-in	No
Marre et al. 2004 Multiple European countries DIABHYCAR Study (GOOD)	Serum creatinine concentration >150 mmol/l; treatment with insulin, an ACE inhibitor, or an angiotensin II receptor blocker; documented congestive chronic heart failure, MI during the past 3 months, urinary tract infection, and previous intolerance to an ACE inhibitor.	Not reported	No

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Control group standard of care?	Funding	Relevance
EUROPA Investigators, 2003; Gomma 2001 Multiple countries in Eastern and Western Europe EUROPA Study	Yes	Sponsored by Servier: Paris, France. Authors received honoraria, research grants, or both from the study sponsor.	Relevant
HOPE Study Investigators, 2000, 1996 Canada, US, Western Europe, Argentina, Brazil, Mexico HOPE Trial	Yes	Funded by the Medical Research Council of Canada, Hoechst-Marion Roussel, Astra-Zeneca, King Pharmaceuticals, Natural Source Vitamin E Association andn Negma, and the Heart and Stroke Foundation of Ontario. First author was supported by a Senior Scientist Award of the Medical Research Council of Canada and a Heart and Stroke Foundation of Ontario Research Chair.	Relevant
Marre et al. 2004 Multiple European countries DIABHYCAR Study (GOOD)	Yes	Supported by a grant from Aventis (Paris) and by a Programme Hospitalier de Recherche Clinique (French Health Ministry).	Low dose of ramipril (1.25 mg day)

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
PEACE Trial Investigators, 2004 Multiple centers in the US (including Puerto Rico), Canada, and Italy	Yes	Method not reported	Yes	Yes	Yes	Yes	Yes
Otsuka et al, 2004 Japan	Yes	Not reported	Yes	Yes	No- open label	No- open label	No- open label
Nissen et al, 2004 Multicenter, US, Canada, and Europe CAMELOT Study	Yes	Yes	Some differences	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating	Number screened/ eligible/ enrolled
PEACE Trial Investigators, 2004 Multiple centers in the US (including Puerto Rico), Canada, and Italy	Attrition and adherence yes crossovers and contamination no	No	Yes	No	Good	# screened not reported/# eligible not reported/8290 enrolled after run-in
Otsuka et al, 2004 Japan	attrition and adherence yes, crossovers and contamination no.	No	Yes	No	Fair	Number screened, eligible not reported/253 enrolled
Nissen et al, 2004 Multicenter, US, Canada, and Europe CAMELOT Study	Attrition yes, others no.	No	Able to calculate (2 in each group not included in efficacy analysis)	No	Fair	2865 screened/ 1997 eligible/ 1997 enrolled

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Exclusion criteria	Run-in/ Washout?	Class-naive patients?
PEACE Trial Investigators, 2004 Multiple centers in the US (including Puerto Rico), Canada, and Italy	Current use of or a current condition requiring use of an ACE inhibitor; contraindication to ACE inhibitors; current use of an angiotensin II-receptor antagonist; hosptialization for unstable angina in the preceding 2 months; valvular heart disease deemed to require surgical intervention; CABG or PTCA in the preceding 3 months; planned elective coronary revascularization; serum creatinine >2.0 mg/dl; serum potassium >5.5 mmol/liter; limited chance of 5-year survival; psychococial condition precluding long-term adherence; unable or unwilling to give consent; female sex and of childbearing potential and not using contraception; current use in a research trial of medication not approved by the US FDA or the Health Protection Branch of the Canadian Department of National Health and Welfare.	2-week run-in with trandolpril 2 mg	No
Otsuka et al, 2004 Japan	Acute major complications, administration of ACE inhibitor for heart failure, medication terminated due to side effects of quinapril, or no follow-up angiography. Acute major complications were defined as Q-wave myocardial infarction, emergency coronary artery bypass graft surgery (CABG) or death in their hospital stay. Myocardial infarction was defined as the occurrence of typical symptoms, electrocardiographic changes and creatine kinase elevation to twice the upper limit of normal. Unstable angina was defined as angina at rest.	No	No
Nissen et al, 2004 Multicenter, US, Canada, and Europe CAMELOT Study	Left main coronary artery obstruction greater than 50%, LVEF less than 40%, or moderate to severe congestive heart failure.	2-week placebo run-in	No

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Control group standard of care?	Funding	Relevance
PEACE Trial Investigators, 2004 Multiple centers in the US (including Puerto Rico), Canada, and Italy	Yes	NHLBI, Knoll Pharmaceuticals, and Abbot Laboratories	Relevant
Otsuka et al, 2004 Japan	Yes	Not reported	Japanese patients, post-PCI
Nissen et al, 2004 Multicenter, US, Canada, and Europe CAMELOT Study	Yes	Pfizer	Relevant

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Kjoller-Hansen et al, 2000, 2004 Single center, Denmark APRES	Yes	Method not reported	Yes	Yes	Yes	Yes	Yes
MacMahon, 2000 Australia and New Zealand PART2	Yes	Yes	Yes	Yes	Yes, but method not described	Not reported	Yes, but method not described
Pitt, 2001, Texter, 1993 US, Canada, Europe QUIET Study	Yes	Method not reported	More prior MI in placebo group (52% vs 47%); more patients in quinapril group taking beta blockers (27% vs 35%) and aspirin (74% vs 71%)	Yes	Yes	Not reported	Yes
Teo, 2000, Teo, 1997 Canada SCAT Trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality Rating	Number screened/ eligible/ enrolled
Kjoller-Hansen et al, 2000, 2004 Single center, Denmark APRES	Attrition and adherence yes, crossovers and contamination no.	No	Yes	No	Fair	3000 screened/213 eligible/159 enrolled (130 after CABG, 29 after PTCA)
MacMahon, 2000 Australia and New Zealand PART2	Attrition yes/crossovers no/adherence yes/contamination yes (reports # of placebo and ramipril patients an ACE inhibitor, but % specifically ramipril not reported)	No	Yes for vital status	No	Fair	Number screened not reported/ 744 eligible/ 617 enrolled
Pitt, 2001, Texter, 1993 US, Canada, Europe QUIET Study	Attrition yes/crossovers no/adherence no/contamination yes	No (4 lost, group not reported)	Yes	No	Fair	Number screened not reported/ number eligible not reported/ 1,750 enrolled
Teo, 2000, Teo, 1997 Canada SCAT Trial	adherence yes	unable to determine	unable to determine	No	Fair	>16,500 charts and 4,000 coronary angiograms screened/ number eligible not reported ("one third of patients entering run-in were not enrolled")/ 460 enrolled/

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Exclusion criteria	Run-in/ Washout?	Class-naive patients?
Kjoller-Hansen et al, 2000, 2004 Single center, Denmark APRES	History of recent acute MI (<3 months), and /or clinical heart failure; I.e., history of dyspnea, relieved by diuretic therapy, ongoing ACEI treatment due to evidenced indications, concomitant valvular disease or geograohic restrictions to complete followup. Participation in another investigational drug trial, known intolerance to ACEI therapy, childbearing potential, and medical conditions (including periprocedural complications) that could have major influence on outcome or known to contraindicate use of the test drug.	Single test dose of ramipril 2.5 mg	No
MacMahon, 2000 Australia and New Zealand PART2	Heart failure or any other definite indication for treatment with an ACE inhibitor, a contraindication to treatment with an ACE inhibitor, serious nonvascular disease, DBP >100 mm Hg, SBP >160 mm Hg or <100 mm Hg during the prerandomizaiton run-in period, or were of childbearing potential without adequate contraception.	Run-in	No
Pitt, 2001, Texter, 1993 US, Canada, Europe QUIET Study	LDL cholesterol >165 mg/dl, coronary artery bypass graft surgery, SBP <100 mm Hg or >160 mm Hg and/or DBP >100 mm Hg; ejection fractin <40%; MI within 7 days; prior angioplasty within 3 months; and those receiving lipid-lowering medications, ACE inhibitors, or calcium channel blockers.	No	No
Teo, 2000, Teo, 1997 Canada SCAT Trial	Within 6 months of coronary angioplasty or bypass surgery; clear indications for or contraindications to study drugs, clinical instability, imminent need for intervention, other significant cardiac or systemic diseases, potential noncompliance, and inability to give informed consent.	Placebo washout	No

Evidence Table 2. Quality assessment of placebo-controlled trials of ACE Inhibitors in patients at high cardiovascular risk

Author, Year Country	Control group standard of care?	Funding	Relevance
Kjoller-Hansen et al, 2000, 2004 Single center, Denmark APRES	Yes	AstraZeneca and Righospitalet, Copenhagen, Denmark.	Post-revascularition patients
MacMahon, 2000 Australia and New Zealand PART2	Yes	Supported by a project grant from Hoeschst AG, the manufacturers of ramipril and by a program grant from the Health Research Council of New Zealand.	Relevant
Pitt, 2001, Texter, 1993 US, Canada, Europe QUIET Study	Yes?	Suppported by Parke-Davis Pharmaceutical Research, Ann Arbor, MI.	Relevant
Teo, 2000, Teo, 1997 Canada SCAT Trial	Yes	Financial and in-kind support from the Medical Research Council of Canada, Merck Frosst Canada & Co, the Alberta Heritage Foundation for Medical Research, University of Alberta Hospitals, and Safeway Canada. The principal investigator has received unrestricted grants from Merck Frosst Canada & Co, as part of the Medical Reserach Council of Canada University-Industry Program. Co-principal investigator is now an employee of Merck Frosst Canada & Co. (was not at the time of the study)	Relevant

Evidence Table 3. Head-to-head trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Eligibility criteria	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Foy (PRACTICAL trial) 1994 New Zealand Fair	A: Captopril 6.25 mg po q 2 hours x 3 doses, then 25 mg tid B: Enalapril 1.25 mg po q 2 hours x 3 doses, then 5 mg tid C: Placebo 12 months	Patients presenting within 24 hours of chest pain with ST segement elevation, new Q waves, or elevation of creatinine phosphokinase	Radionuclide ventriculography Renin-angiotensin levels Mortality Assessed at baseline, 90 days, 12 months	**Captopril vs. enalapril vs. placebo**: Mean age (years): 64 vs. 63 vs. 64 Female gender (%): 16 vs. 16 vs. 7 Race: Not reported	**Captopril vs. enalapril vs. placebo:** Prior MI (%): 17 vs. 13 vs. 11 Beta-blocker at entry (%) 25 (p=0.046) vs. 11 vs. 15 Anterior MI (%): 45 vs. 49 vs. 49 Mean peak CK: 1762 vs. 1949 vs. 1979
Lau 2002 China Fair	A: Captopril 6.25 mg po x 1, then 12.5 mg x 1 2 hours later, then 25 mg x 1 10-12 hours later, then 25 mg po bid x 1 day, then 50 mg po bid B: Perindopril 2 mg po x 1, then 4 mg po qD x 1, then 8 mg po qD 6 months	Aged 18-85 years presenting within 72 hours of acute MI by ECG, creatine kinase, and symptoms criteria	Laboratory screning, ECG, blood pressure monitoring Every 12 hours during the first 48 hours, then at 3 and 6 months	**Captopril vs. perindopril**: Mean age (years): 65 vs. 64 Female gender (%): 19 vs. 28 Race: Not reported	**Captopril vs. perindopril:** Anterior MI (%): 47 vs. 46 Killip class: 1.2 vs. 1.4 Peak CK: 2045 vs. 2020 Beta-blocker use prior to entry (%): 6 vs. 13

Evidence Table 3. Head-to-head trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Foy (PRACTICAL trial) 1994 New Zealand Fair	523 screened 406 eligible 225 enrolled	42 withdrawn Lost to follow-up not clear 167 analyzed	**Captopril vs. enalapril vs. placebo**: Mortality (90 days): 9/75 vs. 1/75 (p=0.038) vs. 7/75 Mortality (12 months): 10/75 vs. 2/75 (p=0.022) vs. 12/75	Not reported	**Captopril vs. enalapril vs. placebo** Withdrawals (overall): 24% vs. 16% vs. 16% Withdrawals (adverse events): Not clear Adverse event requiring dose reduction: 8/75 vs. 4/75 vs. 0/75 Dizziness: 15/75 vs. 14/75 vs. 6/75 Rash: 6/75 vs. 4/75 vs. 0/75 Cough: 6/75 vs. 4/75 vs. 2/75 Loss of taste: 5/75 vs. 1/75 vs. 0/75 GI upset: 2/75 vs. 0/75 vs. 1/75 Headache: 0/75 vs. 1/75 vs. 1/75
Lau 2002 China Fair	Not reported Not reported 212 enrolled	None reported withdrawn or lost to follow-up 212 analyzed	**Captopril vs. perindopril:** Mortality (6 months): 13% (13/102) vs. 6% (7/110) (p=0.12) Revascularization (6 months): 21% (21/102) vs. 20% (22/110) (p=0.9)	Not reported	**Captopril vs. perindopril**: Any adverse events: 17% vs. 13% (NS) Withdrawals (overall): 14% vs. 9% (NS) Hypotension: 3% vs. 2% (p=0.67) Cough: 5% vs. 3% Acute symptomatic hypotension: 7% vs. 2% (p=0.09)

Evidence Table 4. Quality assessment of head-to-head trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Foy (PRACTICAL Trial) 1994 New Zealand	Method not specified	Not described	Significantly more patients on beta-blockers in captopril group	Appears similar	Yes	Method not reported	Method not reported	Not clear
Lau 2002 China	Method not specified	Not described	Significantly higher Killip class (1.4 vs. 1.2, p=0.05) in perindopril group	Appears similar	Yes	Not clear	Not clear	Not clear

Evidence Table 4. Quality assessment of head-to-head trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Foy (PRACTICAL Trial) 1994 New Zealand	Not clear	Yes	No	No	**Fair**	Merck and Bristol-Myers, role not specified	Yes	12 months
Lau 2002 China	Yes	Yes	No	No	**Fair**	Not reported	Yes	6 months

Evidence Table 5. Randomized controlled trials of ACEIs for recent myocardial infarction

Study, year	Interventions	Duration of intervention	Number enrolled	Mortality at end of intervention	Overall quality
Head-to-head trials of one ACE-Inhibitor vs. another ACE-Inhibitor					
Foy (PRACTICAL) 1994	A: Captopril B: Enalapril	12 months	225	13% (10/75) 3% (2/75) (p=0.022)	Fair
Lau 2002	A: Captopril B: Perindopril	6 months	212	13% (13/102) 6% (7/110) (p=0.12)	Fair
Trials of Captopril vs. placebo					
Pfeffer (SAVE) 1992	A: Captopril B: Placebo	Mean 42 months	2231	20% (228/1115) 25% (275/1116) (NS)	Good
Kingma (CATS) 1994	A: Captopril B: Placebo	3 months	298	6% (9/149) 4% (6/149) (NS)	Fair
ISIS-4 1995	A: Captopril B: Placebo	4 weeks	58050	7.2% (2088/29028) 7.7% (2231/29022) (p=0.02)	Good
Shen 1996	A: Captopril B: Placebo	21-22 months	822	In-hospital mortality 7% (33/478) 18% (62/344) (p<0.05)	Fair
Kleber (ECCE) 1997	A: Captopril B: Placebo	4 weeks	208	2% (2/104) 3% (3/104) (NS)	Fair
CCS-1 1997	A: Captopril B: Placebo	4 weeks	6749	9.1% (681/7468) 9.7% (730/7494) (NS)	Fair
Trials of other ACE-Inhibitors vs. placebo					
Swedberg (CONSENSUS II) 1992	A: Enalapril B: Placebo	6 months	6090	10.2% (312/3044) 9.4% (286/3046) (NS)	Good
AIRE 1993	A: Ramipril B: Placebo	6-15 months	2006	17% (170/1004) 23% (222/982) (p=0.002)	Good
Borghi (FAMIS) 1998	A: Fosinopril B: Placebo	3 months	285	8.4% (11/131) 5.2% (7/134) (NS)	Fair
GISSI-3 1994	A: Lisinopril B: Placebo (open)	6 weeks	19394	6.4% (519/9646) 7.2% (693/9672) (p not reported)	Good (not blinded)
Kober (TRACE) 1995	A: Trandolapril B: Placebo	24 months	1749	35% (304/876) 42% (369/873) (p=0.001)	Good

Evidence Table 6. Results of systematic reviews of randomized controlled trials of ACE-Inhibitors from recent myocardial infarction

Trials included in our evidence tables are in bold.

Study	Intervention	Mortality (odds ratio for ACE-Inhibitor vs. placebo)	95% confidence interval
Trials of long-term (>6 weeks) ACEI post-myocardial infarction (Domanski1999)			
AIRE 1993	**Ramipril**	**0.70**	**0.56-0.87**
CATS 1994	**Captopril**	**1.31**	**0.57-3.05**
CONSENSUS 2 1992	**Enalapril**	**1.10**	**0.93-1.31**
ECCE 1997	**Enalapril**	**0.71**	**0.14-3.67**
EDEN 1997	Enalapril	1.48	0.06-36.56
EDI 1997	Enalapril	2.74	0.11-69.15
Mortarino 1990	Captopril	1.10	0.02-60.30
Nabel 1991	Captopril	0.29	0.01-7.44
Oldroyd 1991	Captopril	1.69	0.54-5.36
PRACTICAL 1994	**Enalapril or captopril**	**0.46**	**0.20-1.06**
SAVE 1992	**Captopril**	**0.79**	**0.64-0.96**
Sharpe 1991	Captopril	1.43	0.27-7.61
SMILE 1995	Zofenopril	0.77	0.52-1.12
Sogaard 1994	Captopril	1.00	0.10-10.20
TRACE 1995	**Trandolapril**	**0.73**	**0.60-0.88**
Trials of short-term (<6 weeks) ACEI post-myocardial infarction (Collaborative group,1998)			
ISIS-4 1995	**Captopril**	**0.93**	**0.87-0.99**
CCS-1 1997	**Captopril**	**0.94**	**Not reported**
CONSENSUS 2 1992	**Enalapril**	**1.10**	**0.93-1.29**
GISSI-3 1994	**Lisinopril**	**0.88**	**0.79-0.99**

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Eligibility criteria	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous (AIRE study investigators) 1993 International	A: Ramipril 2.5 mg bid started on day 3-10 after MI for 2 days, then 5 mg bid if tolerated B: Placebo Minimum of 6 months, average 15 months	Over 18 years, admitted to hospital with definite acute MI and clinical evidence of heart failure after MI.	Mortality, clinical evaluation, renal function Clinical evaluation at 4 and 12 weeks after randomization, then every 12 weeks until end of study	Ramipril vs. placebo Mean age (years): 65 vs. 65 Female gender (%): 27 vs. 26 Race: Not reported	Previous MI (%): 29 vs. 27 Diabetes (%): 12 vs. 12 Anterior MI (%): 62 vs. 59 Beta-blocker at entry (%): 24 vs. 21
Anonymous (CCS-1 trial) 1997 China	A: Captopril 6.25 mg po initially, then 12.5 mg po 2 hours later, then 12.5 mg po tid B: Placebo 4 weeks	Patients within 36 hours of the onset of symptoms of suspected acute MI (with or without ST elevation)	Mortality, clinical assessment, ECG Evaluated at baseline, 4 weeks	Captopril vs. placebo Mean age (years): 61 vs. 61 Female gender (%): 26 vs. 26 Race: Not reported, presumed Asian	Previous MI (%): 12 vs. 12 Diabetes (%): 9 vs. 9 Killip class III (%): 9 vs. 9 Killip class IV (%); 3.3 vs. 3.5
Anonymous (GISSI-3) 1994/1996 Italy	A: Lisinopril 5 mg initially, 5 mg after 24 hours, 10 mg after 48 hours, then 10 mg po qD B: Placebo (open) 6 weeks	Chest pain with ST segment changes consistent with acute ischemia, admitted to cardiac care unit within 24 hours of onset of symptoms, and no clear contraindications to interventions	Echocardiography, clinical evaluation, EKG Assessed weekly	Lisinopril vs. placebo Age >70 (%): 27 vs. 27 Female gender (%): 22 vs. 22 Race: Not reported	Previous MI (%): 14 vs. 14 Anterior MI (%): 27 vs. 28 Diabetes (%): 16 vs. 16 IV beta-blockers given (%): 30 vs. 31

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Number screened/ eligible/ enrolled	Outcomes	Method of adverse effects assessment
Anonymous (AIRE study investigators) 1993 International	52019 screened Number eligible about 4000 2006 enrolled	Ramipril vs. placebo Mortality (overall): 17% (170/1004) vs. 23% (222/982) (RRR=27%, p=0.002) First validated events: Mortality: 9% (94/1004) vs. 12% (118/982) Severe or resistant heart failure: 10% (103/1004) vs. 14% (133/982) Reinfarction: 7% (68/1004) vs. 7% (71/982) Stroke: 2% (21/1004) vs. 2% (15/982) Any event: 28% (286/1004) vs. 34% (337/982) (p=0.008)	Serious adverse events pre-defined Adverse events assessed by coordinating center or by independent steering committee
Anonymous (CCS-1 trial) 1997 China	Numbers screened and eligible not reported 14962 enrolled	Captopril vs. placebo Mortality (4 weeks): 9.1% (681/7468) vs. 9.7% (730/7494) (NS) Heart failure: 17% (1272/7468) vs. 19% (1398/7494) (p=0.01) Death or heart failure: 21% vs. 23% (p=0.02) Reinfarction: 5% (362/7468) vs. 5% (350/7494) (NS)	Not specified
Anonymous (GISSI-3) 1994/1996 Italy	43047 screened Number eligible not clear 19394 enrolled	Lisinopril vs. placebo Mortality (6 weeks): 6.4% (619/9646) vs. 7.2% (693/9672) Heart failure: 3.8% vs. 3.7% Ejection fraction <35%: 4.7% vs. 5.5% Combined primary endpoints: 15.5% vs. 16.8% (p=0.04)	Clinical exam, otherwise not clear

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Adverse Effects Reported	Comments
Anonymous (AIRE study investigators) 1993 International	**Ramipril vs. placebo** Withdrawals (overall): 35% (352/1004) vs. 32% (318/982) Withdrawals (adverse events): 13% (126/1004) vs. 7% (68/982) Serious adverse events (including endpoints of the trial): 58% (581/1004) vs. 64% (625/982) Syncope: 2.4% (24/1004) vs. 1.7% (17/982) Hypotension: 4% (42/1004) vs. 2% (23/982) Renal failure: 1.5% (15/1004) vs. 1.2% (12/982) Angina: 18% (181/1004) vs. 17% (171/982)	
Anonymous (CCS-1 trial) 1997 China	Captopril vs. placebo Withdrawals: Not reported Profound hypotension: 8.0% (594/7468) vs. 4.7% (350/7494) (p=0.001) Cough: 5.0% vs. 4.2% (p=0.02) Agranulocytosis: 0.3% vs. 0.1% (p=0.02)	2 year follow-up: Mortality (2 years): 11.9% (404/3391) vs. 13.8% (463/3358) (p=0.03) Reinfarction (2 years): 5.6% vs. 6.0% (p=0.50) Total cardiovascular events (2 years): 33% vs. 34% (p=0.25) (Liu L. Chin Med J 2001;114:115-118)
Anonymous (GISSI-3) 1994/1996 Italy	Lisinopril vs. placebo: Withdrawals: Not reported Persistent hypotension: 9% vs. 4% (p<0.05) Renal dysfunction: 2.4% vs. 1.1% (p<0.05)	Mortality benefits maintained at 6 month follow-up: 9.1% (882/9646) vs. 9.6% (928/9672) Heart failure: 5.4% vs. 5.8% Ejection fraction <35%): 3.3% vs. 3.7% Combined primary endpoints: 18.1% vs. 19.3% (p=0.03) Reinfarction (6 months): 4.7% vs. 4.6% (NS) Angina: 28% vs. 27% (NS) CABG: 4.8% vs. 4.3% (NS) PTCA: 4.0% vs. 3.8% (NS) (Anonymous. J Am Coll Cardiol 1996;27:337-344)

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Eligibility criteria	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous (ISIS-4 collaborative group) 1995 International	A: Captopril 6.25 mg po initially, then 12.5 mg po 2 hours later, then 25 mg po 12 hours later, then 50 mg po bid B: Placebo 28 days	Within 24 hours of onset of symptoms for acute MI with no clear indications for, or contraindications to ACEI, nitrates, or magnesium	Discharge forms and government records for mortality Evaluated at baseline, discharge, and at end of study	Captopril vs. placebo Age >70 (%): 15 vs. 15 Female gender (%): 11 vs. 11 Race: Not reported	Previous MI (%): 9 vs. 11 Anterior ST elevation (%): 8.5 vs. 9.8 IV beta-blocker in hospital (%): 6 vs. 6
Borghi (FAMIS trial) 1998 Italy	A: Fosinopril 5 mg po qD, titrated to 20 mg po qD B: Placebo 3 months (followed up for 2 years)	18-75 years, presented within 9 hours of onset of typical ischemic chest pain associated with ECG changes of definite anterior MI and eligible for thrombolytic treatment	Echocardiography, clinical examination Baseline, at discharge, at 3 onths, and at end of study	Fosinopril vs. placebo Mean age (years): 60 vs. 60 Female gender (%): 22 vs. 13 Race: Not reported	Prevous anterior MI (%): 17% vs. 19% Diabetes (%): 18% vs. 12% Beta-blocker at randomization (%): 7% vs. 10% Killip class II or III (%): 22% vs. 18%

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Number screened/ eligible/ enrolled	Outcomes	Method of adverse effects assessment
Anonymous (ISIS-4 collaborative group) 1995 International	Numbers screened and eligible not reported 58050 enrolled	Captopril vs. placebo Mortality (5 weeks): 7.2% (2088/29028) vs. 7.7% (2231/29022) (p=0.02) Mortality (12 months): 12.0% vs. 12.5% (p<0.01) Angina: 16% vs. 16% CABG or PTCA: 4.6% vs. 4.5% Reinfarction: 4.1% vs. 3.9%	Discharge form evaluated to assess in-hospital adverse events
Borghi (FAMIS trial) 1998 Italy	Number screened and eligible not reported 285 enrolled	Fosinopril vs. placebo Mortality (3 months): 8.4% (11/131) vs. 5.2% (7/134) (NS) Heart failure (3 months): 20% vs. 24% (NS) Mortality or heart failure (3 months): 28% vs. 29% (NS) Ventricular arrhythmia (3 months): 0.8% vs. 6.0% (p=0.02)	Not specified

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Adverse Effects Reported	Comments
Anonymous (ISIS-4 collaborative group) 1995 International	Captopril vs. placebo Withdrawals: Not reported Profound hypotension requiring termination of treatment: 10% vs. 5% (p<0.001) Cardiogenic shock: 4.6% vs. 4.1% (p<0.01) Heart block: 17% vs. 17% Dizziness: 0.5% vs. 0.4% (p<0.01) Renal dysfunction: 1.1% vs. 0.6% (p<0.0001)	Subgroup analysis of diabetic patients (n=2790) found lisinopril associated with decreased 6-week mortality (8.7%) vs. placebo (12.4%) (p<0.05); better (p<0.025) than in nondiabetics (Zuanetti G. Circulation 1997;96:4239-4245). Subgroup analysis of patients with hypertension (n=7362) found no significant benefit for combined end point of mortality or left ventricular dysfunction at 6 weeks (18.0% vs. 18.3%), but did find a significant benefit in normotensives (n=10661) (13.7% vs. 15.8%) (Avanzini F. Am Heart J 2002;144:1018-1025). Benefits of early treatment with lisinopril maintained after 6 months: mortality or severe ventricular dysfunction 18.1% vs. 19.3% (p=0.03) (Anonymous J Am Coll Cariol 1996;27:337-344).
Borghi (FAMIS trial) 1998 Italy	Fosinopril vs. placebo Withdrawals: Not reported Hypotension: 29% vs. 17% (p=0.004) Persistent hypotension requiring treatment or withdrawal of medication: 10% vs. 10% (NS) Cough: 6% vs. 5% Rash: 0% vs. 2% Rise in creatinine: 8% vs. 6% (NS) Hyperkalemia: 5% vs. 4% (NS)	Open-label study after first 3 months; results also reported in Borghi 1997. 2 year follow-up found mortality 14.5% (captopril) vs. 14.1% (placebo) (NS), heart failure 30% vs. 37% (NS), mortality or heartfailure 45% vs. 52% (NS), mortality or NYHA class III or IV heart failure 18% vs. 27% (p=0.04), angina 18% vs. 16% (NS), reinfarction 7.7% vs. 6.7% (NS), PTCA 7.7% vs. 4.5% (NS), and CABGH 3.8% vs. 3.7% (NS)

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Eligibility criteria	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Kingma (CATS trial) 1994 Netherlands	A: Captopril 6.25 mg po after streptokinase infused, then titrated to target dose of 25 mg po tid B: Placebo 3 months	Anterior MI, presenting within 6 hours of onset of symptoms, treated with thrombolytic therapy	Echocardiography, longterm ambulatory ECG, lab evaluation, radionuclide ejection fraction, clinical exam Baseline, , pre-discharge, and 3 months	Captopril vs. placebo Mean age (years): 59 vs. 60 Female gender (%): 30 vs. 20 Race: Not reported	Previous ischemic heart disease (%): 9 vs. 8 Diabetes (%): 9 vs. 9 Killip class I (%): 76 vs. 75 Beta-blocker at randomization (%): 14 vs. 11
Kleber (ECCE trial) 1997 Germany	A: Captopril titrated to mean dose of 66 mg/day at end of 4 weeks B: Placebo 4 weeks	Acute MI, enrolled within 24-72 hours of onset of chest pain	Exercise testing, oxygen uptake testing, mortality Baseline, 4 weeks, 3 months	Captopril vs. placebo Mean age (years): 59 vs. 64 Female gender: 17% vs. 22% Race: Not reported	Previous MI (%): 11% vs. 8% Diabetes: Not reported Anterior MI: 35% vs. 49% (p=0.048) Beta-blocker on admission (%): 11% vs. 14%

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Number screened/ eligible/ enrolled	Outcomes	Method of adverse effects assessment
Kingma (CATS trial) 1994 Netherlands	Numbers screened and eligible not reported 298 enrolled	Captopril vs. placebo Mortality: 6% (9/149) vs. 4% (6/149) (NS) Heart failure: 19% (28/149) vs. 28% (42/149) (p=0.05) Heart failure requiring hospitalization: 1% (2/149) vs. 5% (7/149) (NS) PTCA or CABG: 22% vs. 23% (NS) Reinfarction: 7% (10/149) vs. 3% (4/139) (NS)	Not specified
Kleber (ECCE trial) 1997 Germany	Numbers screened and eligible not reported 208 enrolled	Captopril vs. placebo Death, heart failure requiring ACEI therapy, or VO2max<=10 mL/kg/min (4 weeks): 7% (7/104) vs. 17% (18/104) Death: 2% (2/104) vs. 3% (3/104)	Not specified except that hypotension was closely monitored while in hospital

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Adverse Effects Reported	Comments
Kingma (CATS trial) 1994 Netherlands	Captopril vs. placebo Withdrawals: Not reported Acute hypotension: 21% (31/149) vs. 12% (18/149) Hypotension (3 months): 27% vs. 18% (NS)	12 month follow-up study (van den Heuvel, A. F. M. J Am Coll Cardiol 1997;30:400-5) (n=244) Ischemia related events by 12 months (PTCA, CABG, MI, angina, death): 34% (38/112) vs. 42% (56/132) (NS) Death: 2% (2/112) vs. 2% (3/132) Reinfarction: 2% (2/112) vs. 2% (2/132) Ischemia related events from 3-12 months: 18% (20/112) vs. 32% (42/132) (p=0.018) 12 month follow-up study (van Gilst, W. H. J Am Coll Cardiol 1996;28:114-21) (n=298) Mortality: 9% (13/149) vs. 7% (10/149) Heart failure: 26% (39/149) vs. 36% (53/149) (p<0.03) Reinfarction: 10% (15/149) vs. 4% (6/149) CABG: 8% (12/149) vs. 7% (11/149) PTCA: 23% (34/149) vs. 28% (42/149) Any clinical event: 58% (86/149) vs. 62% (92/149) 12 month follow-up study (Hillege, H.L. Eur Ht Jl 2003;24:412-20) (n=298) Mean decline in GFR (ml/min): 0.5 vs. 5.5 (p<0.05)
Kleber (ECCE trial) 1997 Germany	Captopril vs. placebo Withdrawal (overall): 4% vs. 12% Withdrawal (adverse events): Not reported First dose hypotension: 37% vs. 18% (p<0.05) Adverse events possibly, likely, or definitely related to therapy: 36% vs. 30% 'Severe' adverse events: 17% vs. 17% Diastolic blood pressure <60: 22% vs. 12%	

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Eligibility criteria	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Kober (TRACE trial) 1995 Europe	A: Trandolapril 1 mg po qD started 3-7 days after MI, then 2 mg qD after 2 days, then 4 mg qD after 4 weeks B: Placebo 24 months	Over 18 years, hospitalized with myocardial infarction by clinical symptoms or typical ECG changes, accompanied by increase in cardiac enzymes, evaluated between day 2 and 6 after onset of symptoms, and ejection fraction less than 35%	Mortality end-point committee, reinfarction end-point committee Baseline, 3 months, 6 months, 1 year, 2 years	Trandolapril vs. placebo Mean age (years): 68 vs. 67 Female gender (%): 28 vs. 29 Race: Not reported	Prevoius MI (%): 37 vs. 34 Diabetes (%): 13 vs. 14 Anterior Q wave (%): 47 vs. 47 Kilip class >=2 (%): 21 vs. 21 Beta-blocker (%): 17 vs. 15
Pfeffer (SAVE trial) 1992 United States	A: Captopril 12.5 mg po tid titrated to 50 mg po tid B: Placebo Mean 42 months	21-80 years, survived 3 days after MI, left ventricular ejection fraction <40%	Mortality, clinical evaluation, renal function Evaluated at baseline, every 2 weeks after randomization, every 3 months during year 1, and every 4 months after year 1	Captopril vs. placebo Mean age (years): 59 vs. 59 Female gender (%): 17 vs. 18 Race: Not reported	Previous MI (%): 36 vs. 35 Diabetes (%): 21 vs. 23 Killip class I (%): 60 vs. 59 Anterolateral Q wave (%): 56 vs. 54 Beta-blockers within 24 hours of randomization (%): 35 vs. 36

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Number screened/ eligible/ enrolled	Outcomes	Method of adverse effects assessment
Kober (TRACE trial) 1995 Europe	7001 myocardial infarctions in 6676 patients screened 2606 eligible 1749 enrolled	Trandolapril vs. placebo Mortality (2 years): 34.7% (304/876) vs. 42.3% (369/873) (p=0.001) Progression to severe heart failure: 14% (125/876) vs. 20% (171/873) (p=0.003) Reinfarction: 11% (99/876) vs. 13% (113/873) (p=0.29)	Not specified
Pfeffer (SAVE trial) 1992 United States	Numbers screened and eligible not reported 2231 enrolled	Captopril vs. placebo Mortality: 20% (228/1115) vs. 25% (275/1116) (p=0.02) Revascularization: 14% (154/1115) vs. 17% (195/1116 (p=0.10) Hospitalization for unstable angina: 12% (135/1115) vs. 12% (133/1116) (p=0.930) Clinical MI, revascularization, or hospitalization for unstable angina: 29% (327/1115) vs. 33% (363/1116) (p=0.47) Heart failure requiring open-label ACEI: 11% vs. 16% (p=0.001) Heart failure requiring hospitalization: 14% vs. 17% (p=0.019) Mortality or heart failure or non-fatal MI: 32% vs. 40% (p<0.01)	Not specified

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Adverse Effects Reported	Comments
Kober (TRACE trial) 1995 Europe	Trandolapril vs. placebo Withdrawal (overall): 37% (328/876) vs. 36% (310/873) Withdrawal (adverse events): Not clear Angina: NS Chest pain: NS Pneumonia: 10% vs. 15% (p=0.001) Cough: 34% vs. 21% (p<0.001) Hypotension: 31% vs. 22% (p<0.001) Renal dysfunction: 14% vs. 11% (p=0.06) Hyperkalemia: 5% vs. 3% (p=0.01)	Long-term follow-up (minimum 6 years) found increased median lifetime on trandolapril 15.3 months (95% confidence interval 7 to 51); Torp-Pedersen, C.T. Lancet 1999; 354: 9-12. In diabetics (n=347) relative risk of death in group on trandolapril 0.64 (95% CI 0.45 to 0.91) compared to placebo, versus 0.82 (0.69 to 0.97) nondiabetics. Trandolapril reduced the risk of progression to severe heart failure in diabetics (RR 0.38 [0.21 to 0.67]) but not in nondiabetics; Gustafsson I. J Am Coll Cardiol 1999; 34: 83-9. Lower proportion of patients (44%) received thrombolytics than in placebo-controlled trials of other ACEIs.
Pfeffer (SAVE trial) 1992 United States	Captopril vs. placebo Withdrawal (overall): Not reported Withdrawal (adverse events): 6% (68/1115) vs. 3% (39/1116) Significantly more common in captopril arm: Dizziness: 5% Alteration in taste: 2% Cough: 6% Diarrhea: 2%	Additional results published in Rutherford 1994

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Eligibility criteria	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Shen 1996 China	A: Captopril 6.25 mg initially, then titrated to 12.5-25 mg tid B: Placebo 21-22 months	Presentation within 72 hours of onset of symptoms and no cardiogenic shock	Clinical evaluation Assessed at baseline and every 1-3 months	Captopril vs. placebo Mean age (years): 64 vs. 63 Female gender (%): 23 vs. 26 Race: Not performed, presumed Asian	Captopril vs. placebo Previous MI (%): Not reported Diabetes (%): 10% vs. 13% Anterior MI (%): 55% vs. 51% Beta-blocker (%): 51% vs. 70%
Swedberg (CONSENSUS II trial) 1992 Scandinavia	A: Enalapril at 1 mg IV over 2 hours, then enalapril 2.5 mg po bid starting 6 hours after IV dose, titrated to 20 mg po qD B: Placebo 6 months	Presentation within 24 hours of the onset of chest pain due to acute myocardial infarction with typical EKG changes or elevated cardiac enzymes	Clinical assessment, end-point committee, independent safety committee Baseline, 1 month and 6 months	Enalapril vs. placebo Mean age (years): 66 vs. 66 Female gender (%): 27 vs. 26 Race: Not reported	Enalapril vs. placebo Previous MI (%): 23 vs. 24 Diabetes (%): 12 vs. 11 Anterior MI (%): 42 vs. 41 Beta-blockers before randomization (%): 66 vs. 67

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Number screened/ eligible/ enrolled	Outcomes	Method of adverse effects assessment
Shen 1996 China	Number screened and eligible not reported 822 enrolled	Captopril vs. placebo Mortality (in-hospital): 7% (33/478) vs. 18% (62/344) (p<0.05) Mortality (21-22 months): Rates not reported, survival curves significantly better in captopril group Heart failure: 5.5% (21/383) vs. 10.9% (31/284) (p not reported)	Not reported
Swedberg (CONSENSUS II trial) 1992 Scandinavia	10387 screened Number eligible not clear 6090 enrolled	Enalapril vs. placebo Mortality: 10.2% (312/3044) vs. 9.4% (286/3046) (p=0.26) >=1 hospitalization for heart failure: 4% (130/3044) vs. 6% (174/3046) (NS) Change of therapy because of heart failure: 27% vs. 30% (p<0.006) Reinfarction: 9% (271/3044) vs. 9% (268/3046) (NS)	Independent safety committee, otherwise not clear

Evidence Table 7. Placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Adverse Effects Reported	Comments
Shen 1996 China	Not reported	
Swedberg (CONSENSUS II trial) 1992 Scandinavia	Enalapril vs. placebo Withdrawal (overall): 18% (538/3044) vs. 12% (374/3046) (p<0.001) Withdrawal (adverse events): 9.7% (296/3044) vs. 4.5% (138/3046) (p<0.001) Hypotension below 90/50 initially: 12% vs. 3% (p<0.001) Any adverse event: 74% vs. 70% (p<0.001) Angina: 14% vs. 15% (NS) Hypotension (at any time): 25% vs. 10% (p<0.001) Heart failure: 25% vs. 28% (p=0.012) Increased creatinine: 2.4% vs. 1.0% (p<0.001) Diarrhea: 1.5% vs. 0% (p=0.024) Cough: 6.8% vs. 3.1% (p<0.001)	Trial stopped early because of high likelihood that the null hypothesis would apply. Quality of life (Nottingham Health Profile, Physical symptoms distress Index, Work Performance Scale, and the Life Satisfaction Index) on enalapril after acute MI not significantly different than placebo in substudy of 132 patients 4-6 months after MI (Ekebert, O. Eur Ht Journal 1994; 15: 1135-1139).

Evidence Table 8. Quality assessment of placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	How many recruited?	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Anonymous (AIRE study investigators) **1993** International	Randomization code, numbers allocated in blocks of ten	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes
Anonymous (CCS-1 trial) **1997** China	Computer generated	Not specified	Yes	Yes	14962 screened	Yes	Not clear	Not clear	Not clear
Anonymous (GISSI-3) **1996** Italy	Computer generated	Not specified	Yes	Yes	43047 screened	Yes	No	No	No
Anonymous (ISIS-4 collaborative group) **1995** International	Computer generated	Not specified	Yes	Yes	NR	Yes	Yes	Yes	Yes
Borghi (FAMIS trial) **1997** Italy	NR	Not specified	No, fosinopril group had more severe heart failure	Yes	NR	Yes	No, after 3 months	No, after 3 months	No, open-label after 3 months
Kingma (CATS trial) **1994** Netherlands	NR	Not specified	Yes	Yes	NR	Yes	Yes	Yes	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Anonymous (AIRE study investigators) **1993** International	Yes	Yes	Yes	No	**Good**	Hoechst, not clear if data held by funder	Yes	6-15 months
Anonymous (CCS-1 trial) **1997** China	Yes	Yes	No	Not clear	**Fair**	None reported	Yes	2 years
Anonymous (GISSI-3) **1996** Italy	Yes	Yes	Yes	No	**Good (not blinded)**	Zeneca pharmaceutical	Yes	6 weeks
Anonymous (ISIS-4 collaborative group) **1995** International	Yes	Yes	Yes	No	**Good**	None reported	Yes	12 months
Borghi (FAMIS trial) **1997** Italy	Yes	Not clear	No	Not clear	**Fair**	Bristol-Myers	Yes	2 years
Kingma (CATS trial) **1994** Netherlands	Yes	Yes	Yes	No	**Fair**	Bristol-Myers	Yes	3 months

Evidence Table 8. Quality assessment of placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	How many recruited?	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Kleber (ECCE trial) **1997** Germany	Blocks of six, otherwise not reported	Not specified	Yes	Yes	NR	Yes	Not clear	Yes	Not clear
Kober (TRACE trial) **1995** Europe	Computer generated	Not specified	Yes	Yes	6676 screened	Yes	Yes	Yes	Yes
Pfeffer (SAVE trial) **1992** United States	Computer generated	Not specified	Yes	Yes	NR	Yes	Not clear	Not clear	Not clear
Shen (Shanghai Second Prevention of AMI trial)	NR	Not specified	No, captopril had more patients on beta-blockers	Yes	NR	Yes	Not clear	Not clear	Not clear
Swedberg (CONSENSUS II trial) **1992** Scandinavia	Stratified in blocks of 2 to 10	Not specified	Yes	Yes	10387 screened	Yes	Yes	Not clear	Not clear

Evidence Table 8. Quality assessment of placebo-controlled trials of ACE-Inhibitors for recent myocardial infarction

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Kleber (ECCE trial) **1997** Germany	Yes	Yes	Yes	No	**Fair**	Schwarz Pharma	Yes	4 weeks
Kober (TRACE trial) **1995** Europe	Yes	Yes	Yes	No	**Good**	Roussel-Uclaf and Knoll	Yes	24-50 months
Pfeffer (SAVE trial) **1992** United States	Yes	Yes	Yes	No	**Good**	Bristol-Myers, did not hold data	Yes	42 months
Shen (Shanghai Second Prevention of AMI trial)	Not clear	Not clear	Yes	High overall loss to follow-up (19% overall)	**Fair**	None reported	Yes	21-22 months
Swedberg (CONSENSUS II trial) **1992** Scandinavia	Yes	Yes	Yes	No	**Good**	Merrck Sharp and Dohme Research Laboratories	Yes	6 months planned, trial stopped early

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Acanfora 1997 Italy Multicenter (Fair)	65 Quinapril 66 Captopril	A: Quinapril 10 mg once daily for 4 weeks, then titrated to 20 mg once daily on physician judgment if no major adverse reactions and if BP not < 110/70. B: Captopril 12.5 mg BID for 4 weeks, then titrated to 25 mg BID on physician judgment if no major adverse reactons and if BP not <110/70. 12 weeks	
Bach 1992 Germany, Italy Multicenter (Poor)	148 Lisinopril 139 Captopril	A: Lisinopril 5 mg once daily, increased to 10 mg at 2 weeks and 20 mg at 4 weeks if no hypotension and if need for additional therapeutic effect. Dose reduced if hypotension or other adverse event occurred. B: Captopril 12.5 mg BID, increased to 25 mg BID at 2 weeks and 50 mg BID at 4 weeks if no hypotension and if need for additional therapeutic effect. Dose reduced if hypotension or other adverse event occurred. 12 weeks	Over age 21 with HF Class II and III, capable of exercise protocol 4-12 minutes, symptomatic on stable doses of digitalis or diuretics or both.
Beynon 1997 Open Single center (Poor)	31 Captopril 30 Quinapril	A: Captopril titrated every 2 weeks to 16-week maintenance phase: 6.25 mg BID, 12.5 mg BID, 25 mg BID, 50 mg BID. B: Quinapril titrated every 2 weeks to 16-week maintenance phase: 2.5 mg once daily, 5 mg once daily, 10 mg once daily, 20 mg once daily. 16 weeks after 2 to 8 weeks titration.	Over age 64, weight >45 kg, NYHA Class II or III with etiology of ischemic heart disease, ambulatory, stable, on maintenance diuretics not exceeding 80 mg frusemide per day or equivalent.

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Baseline NYHA Class
Acanfora 1997 Italy Multicenter (Fair)	NR.	Clinical exam during 2-week run-in and every 2 weeks during treatment. BP, clinical signs and symptoms recorded and patients classified according to NYHA class. Exercise test at tend of run-in and after 4 and 12 weeks of treatment. Self-reports of adverse effects.	Quinapril vs Captopril: Mean Age 61.5 (sd 8.6) vs 61.3 (sd 10) 77% vs 75% male Ethnicity NR	Quinapril vs Captopril: Class I: 0% vs 1.5% Class II: 65% vs 69% Class III: 35% vs 29%
Bach 1992 Germany, Italy Multicenter (Poor)	Placebo baseline of 10-14 days during which time digoxin and/or diuretic doses optimized, all other vasodilator and ACE Inhibitors withdrawn.	Physical exam at entry, abbreviated symptom review and physical exam at randomization and at end (12 weeks). Exercise testing with bicycle ergometer, 2 tests during run-in, at 6 and 12 weeks of treatment. NYHA class assessment done by same observer at end of run-in and at end.	Lisinopril vs Captopril: Mean age 59 (29-83) vs 59 (33-82) 79% vs 78% male Ethnicity NR	Baseline NYHA Class NR Etiology of heart failure, Lisinopril vs Captopril: Ischemic heart disease: 52% vs 49% Cardiomyopathy: 35% vs 41% Valvular heart disease: 14% vs 8% Hypertension: 22% vs 18% Other: 9% vs 5%
Beynon 1997 Open Single center (Poor)	NR.	6-minute walking measures and functional life-scale assessment	NR. States no statistically significant differences between treatment groups at baseline regarding age, sex, race.	(Reported for only 36 evaluable patients): Captopril vs Quinapril: Class II: 63% vs 75% Class III: 38% vs 25%

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed	Results	Adverse Effects Reported
Acanfora 1997 Italy Multicenter (Fair)	# screened NR # eligible NR 131 enrolled	2 withdrew 1 died 131 analyzed	Quinapril vs Captopril NYHA Class at Week 12: Class I 8% vs 3% (p=NS) Class II 86% vs 75% (p=NS) Class III 6% vs 22% (p<0.05) Exercise duration (minutes) at week 12: 7.8 ± 1.9 vs 7.1 ± 2.3 (p=NS) Stopped exercise test due to fatigue: 32% vs 26% (p NR)	Quinapril: 1 patient died suddenly, 0 patients reported side effects. Captopril: 2 dropped out due to persistent dry cough, 3 patients moderate dry cough, 1 taste blindness, 1 unstable angina.
Bach 1992 Germany, Italy Multicenter (Poor)	# screened NR 315 eligible 287 enrolled	38 withdrew 252 analyzed	Lisinopril vs Captopril NYHA Class: 35% vs 40% showed improvement 63% vs 58% no change 1.6% vs 1.6% deteriorated (p-values NR) Exercise capacity: after 12 weeks, exercise duration increased by both. Increase slightly greater for Lisinopril, but NS (5 seconds, p=0.68) Symptom review and physical exam: regarding % of patients improving, effect similar for both.	Lisinopril vs Captopril Adverse events reported: 16% vs 15% (p= NS) Withdrawals due to adverse events (including death): 6% vs 5% (p=NS) 5 deaths vs 2 deaths Cause of death: pulmonary edema, ventricular fibrillation, sudden death (n=2), accident vs cardiac failure after MI, pulmonary edema Adverse events not leading to withdrawal: 10% vs 11%
Beynon 1997 Open Single center (Poor)	# screened NR # eligible NR 61 enrolled	23 withdrew 2 lost to followup 36 analyzed	Captopril vs Quinapril NYHA Class 23% deteriorated, 68% no change, 10% improved vs 0% deteriorated, 83% no change, 17% improved (p=0.02) Six-minute walking test, mean improvement in distance walked 83.1 meters vs 72.2 meters (p=0.84) Functional life scale mean changes NS (p=0.86) cardiothoracic ratio 1.2% decrease vs 0.3% decrease (NS clinically or statistically)	Captopril vs Quinapril: Number of adverse events 71 (18 considered treatment-related) vs 76 (28 considered treatment-related)

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	182 Cilazapril 87 Captopril	A: Cilazapril 0.5 mg once daily for 1 week, then increased to 1 mg once daily. If inadequate response after 4 weeks, increased to 2.5 mg once daily. B: Captopril 6.25 mg three times daily, then increased to 25 mg three times daily. If inadequate response after 4 weeks, increased to 50 mg three times daily.	NYHA Class II, III, or IV, clinically stable on digoxin and/or diuretics, over age 18.
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	221 Cilazapril 108 Captopril	A: Cilazapril 0.5 mg once daily for one week, then 1 mg up to week 4; if no improvement increased to 2.5 mg once daily B: Captopril 6.25 mg TID for one week, then 25 mg TID up to week 4; if no improvement increased to 50 mg TID. 24 weeks	HF NYHA classes II-IV, 18 years or older, chronic HF (onset >3 months), and clinically stable on digitalis and/or diuretics.

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Baseline NYHA Class
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	Digoxin and/or diuretics.	Quality of life questionnaires: sickness impact profile (SIP), profile of mood states(POMS), other questions to assess dyspnea and ascertain the impact of ill health on leisure and regular activities. Health Status Index (HSI) calculated from questionnaire responses. Assessed at entry, after 12 weeks, and 24 weeks, or at the final visit whenever possible. Self-administered except for Mahler index of dyspnea.	Mean age 63 years (range 21-87) 64% male Ethnicity not reported (states no differences between groups)	Class II: 62% Class III: 36% Class IV: 1% (states no difference between groups)
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	Digitalis.	Exercise test on a bicycle ergometer and 6-minute walking test at baseline, repeated at 4, 8, 12, and 24 weeks. Clinical status, including NYHA class, assessed during each visit.	Cilazapril vs Captopril: mean age 63.0 (range 32-87, SD 10.1) vs 62.2 (range 21-85, SD 11.6) 67% vs 63% male 100% vs 99% white	Cilazapril vs Captopril: Class II: 62% vs 56% Class III: 36% vs 42% Class IV: 1% vs 2% Missing: 0.5% vs 0

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed	Results	Adverse Effects Reported
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	# screened NR # eligible NR 443 enrolled	76 incomplete data 367 analyzed	Cilazapril vs Captopril **Sickness Impact Score mean change from baseline at 12 weeks (scale 0-48):** -2.29 vs -2.93 (NS) **Profiile of Mood States mean change from baseline at 12 weeks (scale 0-149):** -5.46 vs -7.34 (NS) **Health Status Index mean change from baseline at 12 weeks (+ = improvement):** +0.04 vs +0.04 (NS)	Not reported
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	# screened NR # eligible NR 443 analyzed	22% cilazapril and 25% captopril withdrew lost to followup not reported # analyzed not clear	Cilazapril vs Captopril: Increase in exercise duration (seconds) from baseline to week 12: 62.7 ± 0.06 vs 73.1 ± 2.4 (NS) From baseline to week 24: 81.2 ± 2.2 vs 80.3 ± 3.5 (NS) Increase in distance in 6-minute walk test from baseline to week 12: 33 ± 4 vs 30 ± 6 From baseline to week 24: 44 ± 5 vs 35 ± 8 Improvement by at least one NYHA class at 24 weeks: 35% vs 36% (NS)	Cilazapril vs Captopril: Patients reporting one or more adverse events at week 12 41.6% vs 40.7%; at week 24 52.5% vs 54.6% Most frequent dizziness (10.0% vs 10.2%) and coughing (9.0% vs 9.3%). For captopril, elderly patients had more adverse events (63.0%) than younger patients (48.4%); cilazapril no difference by age group. Withdrawals due to adverse effects 5.4% vs 13.0% 8 deaths (0.8% placebo, 2% cilazapril, 1.8% captopril)

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
de Graeff 1989 The Netherlands Open Single center (Poor)	7 Ramipril 5 Captopril	A: Ramipril 5 mg initially, then after 24 hours 10 mg once daily unless symptomatic hypotension occurred; when clinical response unsatisfactory, dose adjusted to maximum of 10 mg BID. B: Captopril 12.5 mg initially, then after 24 hours 25 mg TID unless symptomatic hypotension occurred; when clinical response unsatisfactory, dose adjusted to maximum of 50 mg TID. 12 weeks	Hospitalized patients with chronic HF NYHA Class III-IV, with severe restriction of physical activity or symptoms of dyspnea or fatigue at rest for more than 3 months despite adequate treatment with salt restriction, diuretics, and digoxin.
Dirksen 1991 The Netherlands Open Multicenter (Poor)	19 Enalapril 21 Captopril	A: Enalapril 10 mg once daily for 2 weeks, then depending on response, either maintained, decreased to 5 mg once daily or increased to 20 mg once daily. B: Captopril 12.5 mg TID for 2 weeks, then depending on response, maintained, decreased to 6.5 mg TID or increased to 25 mg TID. 3 months	NYHA Class II or III.
Gavazzi 1994 Italy Multicenter (Fair)	76 Quinapril 70 Captopril	A: Quinapril 10 mg once daily, after 4 weeks of treatment, doses titrated to 20 mg once daily as required to maintain adequate BP control without sitting BP falling below 110/70 or other major adverse events. B: Captopril 25 mg BID, after 4 weeks of treatment, doses titrated to 50 mg BID as required to maintain adequate BP control without sitting BP falling below 110/70 or other major adverse events. 12 weeks	Over age 40 with Class I-III HF

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Baseline NYHA Class
de Graeff 1989 The Netherlands Open Single center (Poor)	Treatment with salt restriction, diuretics, and digoxin was maintained.	Patients were initially hospitalized, discharged after reaching a clinically stable condition and seen every 3 weeks as outpatients. Symptoms evaluated using the NYHA score.	Ramipril vs Captopril: mean age 70 (62-76) vs 58 (48-81) 86% vs 100% males Ethnicity NR	Ramipril vs Captopril: Class III: 29% vs 60%, Class III-IV: 43% vs 40% Class IV: 29% vs 0%
Dirksen 1991 The Netherlands Open Multicenter (Poor)	Other cardiovascular agents except digitalis, diuretics, and sublingual nitroglycerin discontinued at start of run-in. Doses not altered. Treatment with potassium-sparing diuretics not allowed during treatment.	NYHA class measured at week -2, -1, 0, 2, 4, 6, 8, 10, 12, and bicycle ergometric tests at weeks 0, 2, 12.	Enalapril vs Captopril: Mean age 61 (range 31-77) vs 61 (range 46-74) 68% vs 76% males Ethnicity NR	Enalapril vs Captopril: Class II: 58% vs 48% Class III: 42% vs 52%
Gavazzi 1994 Italy Multicenter (Fair)	Any baseline diuretic and/or digitalis therapy was maintained at the same dose during washout and treatment period.	Clinical signs and symptoms, exercise capacity, EKG, all performed at end of washout and during week 12 of treatment. Classification of HF by NYHA criteria determined by investigators at each clinical visit.	Captopril vs Quinapril Mean age 59.9 (sd 9.0, range 41-79) vs 62.2 (sd 7.9, range 47-79) 73% vs 75% males	Captopril vs Quinapril Class I: 23% vs 12% Class II: 50% vs 72% Class III 27% vs. 14%

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed	Results	Adverse Effects Reported
de Graeff 1989 The Netherlands Open Single center (Poor)	# screened NR # eligible NR 13 enrolled	1 withdrew 12 analyzed	Ramipril vs Captopril, Improvement by at least 1 NYHA Class: 58% vs 40%	3 deaths (2 Ramipril, 1 Captopril) 1 patient not analyzed- found to have hyperthyroidism after 6 weeks of Captopril. 1 patient (Ramipril) discontinued after 1st dose due to catheter sepsis. 1 patient (Captopril withdrawn after 9 weeks because of progression of heart failure. 3 patients developed symptomatic hypertension with dizziness, blurred vision, and sleepiness (2 Ramipril, 1 Captopril) 1 Patient (Captopril) developed itching and mild rash.
Dirksen 1991 The Netherlands Open Multicenter (Poor)	# screened NR 52 eligible 40 enrolled	0 withdrew 0 lost to followup 40 analyzed	Enalapril vs Captopril, NYHA Class at week 12: Class I 16% vs 14% Class II 63% vs 57% Class III 21% vs 19% Class IV 0% vs 10% Improvement from baseline statistically significant (p=0.02) only in Enalapril group Improvement by at least 1 class: 37% vs 33%	Enalapril vs Captopril: Drug-related adverse effects: 17 vs 16 events worsening of NYHA class 0% vs 10%
Gavazzi 1994 Italy Multicenter (Fair)	# screened NR # eligible NR # enrolled NR	# withdrawn NR # lost to followup NR 146 analyzed	Captopril vs Quinapril Improvement in NYHA class 27.1% vs 24.0% (NS) Increase in exercise duration, baseline to week 12: 451.7 to 519.0 sec vs 422.1 to 497.2 sec (p < 0.05 for both Captopril and Quinapril) Improvement in symptoms at 12 weeks Captopril vs Quinapril Any sign of HF 27.1% vs 41.3% (NS) dsypnea at rest 45.4% vs 80.0% (NS) dsypnea at effort 40.9% vs 39.2% (NS) orthopnea 66.7% vs 50.0% peripheral edema 61.1% vs 72.0% (NS) lung congestion 57.1% vs 86.4% (p=0.03)	Captopril: 12 adverse events in 9 patients vs Quinapril 11 adverse events in 9 Quinapril patients 7 vs 5 considered drug-related Most frequent drug-related adverse event was hypotension (3 Captopril vs 2 Quinapril)

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Giles 1988, 1989 US Multicenter (Fair)	94 Lisinopril 95 Captopril Subgroup of patients over age 65: 37 Lisinopril 28 Captopril	A: Lisinopril 5 mg once daily, increased if needed at 4-week intervals unless symptomatic hypotension occurred. Titration doses 5 mg, 10 mg, 20 mg once daily. B: Captopril 12.5 mg TID, increased if needed at 4-week intervals unless symptomatic hypotension. Titration doses 12.5 mg, 25 mg, 50 mg TID. 12 weeks	Age 18 or older, NYHA Class II, II, or IV, able to exercise 1-12 minutes on a treadmill.
Haffner 1995 UK Multicenter (Poor)	41 Captopril 39 Enalapril	A: Captopril 12.5 mg BID B: Enalapril 2.5 mg BID 6 months	Over age 65, heart failure defined by 2 or more: Tachycardia, gallop rhythm, increased jugular vein pressure, bilateral basal crepitations or auscultaton of the lungs, peripheral edema, and or evidence of heart failure on chest x-ray. Required 40-80 mg frusemide daily.

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Baseline NYHA Class
Giles 1988, 1989 US Multicenter (Fair)	All antihypertensive and vasodilator medications withdrawn. Doses of digoxin were maintained constant throughout the study period. Doses of diuretics could be adjusted for clinical reasons during the study.	Treadmill exercise tests: 2 during baseline and 23 (at 4-week intervals) during study. Lab screening at baseline and 4-week intervals. Clinical evaluation at 4-week intervals and 2 weeks after each dose adjustment	Lisinopril vs Captopril Mean age 61.3 vs. 59.1 76% vs. 81% male, 24% vs 29% black In sub-analysis of those > age 65 (Giles 1988): Mean age 71 vs 70 81% vs 82% male Ethnicity NR	Lisinopril vs Captopril Class II 31% vs 31% Class III 61% vs 62% Class IV 8% vs 7%
Haffner 1995 UK Multicenter (Poor)	Not clear, frusemide allowed; decreased to 40 mg if dose was 80 mg	Baseline assessments: BP and pulse, blood tests, ECG, chest X-ray, exercise test, symptom-oriented questionnaire, hemodynamic tests, blood test, and questionnaire repeated at 1 week; further complete assessments at 3 and 6 months. Patients were visited monthly to deliver meds and assess compliance by tablet count. Walking test in 25 patients at one center. Quality of life and minor adverse effects assessed by questionnaire at one center.	Captopril vs Enalapril Mean age 77 (66-93) vs 75.3 (65-93) Sex NR Ethnicity NR	NYHA Class NR. Clinical signs, Captopril vs Enalapril: Tachycardia 39% vs 54% Gallop rhythm 66% vs 79% Raised jugular vein pressure 32% vs 44% Pulmonary edema 76% vs 69% Edema 58% vs 49%

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed	Results	Adverse Effects Reported
Giles 1988, 1989 US Multicenter (Fair)	# screened NR # eligible NR 189 enrolled	# withdrawn NR # lost to followup NR 189 analyzed	Lisinopril vs Captopril Change in NYHA Class 30% vs 31% improved 0% vs 3% deteriorated Mean increase in exercise duration at week 12 137 sec vs 120 sec (p=NS) Subgroup of patients over age 65 (Giles 1988): Lisinopril vs Captopril Change in NYHA Class 24% vs 26% improved, 76% vs 74% unchanged, 0% vs 0% worse (p NR) Mean change in exercise duration 134.3 sec vs 71.8 sec (p=0.08)	35.1% of L and 47.4% of C had clinical adverse experiences (p=NS). 3 C died, 0L died. 11.6% of C and 3.2% of L had serious adverse effects. 2 patients in each group had adverse effects considered severe and/or requiring discontinuation of therapy: Symptomatic dizziness requiring discontinuation of therapy occurred in 1 patient in each group. Captopril Discontinued in 1 patients due to severe taste disturbance, and Lisinopril discontinued in 1 patient due to worsening hepatic and renal function. Subgroup analysis: L- 51%, C- 54% had 1 or more AE; serious AE: L- no deaths, 1 GI pain; C- 1 death, 1 hypotension, 1 cerebrovascular disease, 1 hypertensive crisis
Haffner 1995 UK Multicenter (Poor)	# screened NR 96 eligible 80 enrolled	24 withdrawn 0 lost to followup 56 analyzed	Walking tests (performed on 25 patients only) improvement in both groups after 3 months. Trend to further improvement at 6 months in Captopril group (0.54 m/s, sd 0.14) but not in Enalapril group (0.49 m/s, sd 0.28). Differences between groups NS, p NR	By questionnaire (of 45 patients only)- GI complaints 9/14 Enalapril (64%) vs 2/14 Enalapril (11%), p=0.039 30% (24/80) patients withdrawn after randomization. Reasons for withdrawal, Captopril vs Enalapril death (sudden) 3(1) vs 3(3) ineffective 2 vs 1 poor compliance 1 vs 1 symptomatic hypotension 0 vs 4 other adverse effects 5 vs 0 anemia 1 vs 0 on non-permitted drug 1 vs 0 cardiac surgery 0 vs 1 proteinuria 0 vs 1 renal impairment 0 vs 1 patient request 0 vs 1 cough 0 vs 1 total events 13 vs 14

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Morisco 1997 Italy Multicenter (Fair)	128 Lisinopril 123 Captopril	A: Lisinopril 5 mg once daily increased to 10 mg after 2 weeks if SBP >90, no symptoms of hypotension, and if need for additional therapeutic effect, increased to 20 mg after 2 weeks if above criteria met. Dose decreased if symptomatic hypotension or any other drug-related adverse effects. B: Captopril 12.5 mg once daily, increased to 12.5 mg BID after 2 weeks if SBP >90, no symptoms of hypotension, and if need for additional therapeutic effect, then increased to 25 mg BID after 2 weeks if above criteria met. Dose decreased if symptomatic hypotension or any other drug-related adverse effects. 12 weeks	Ages 65-80, NYHA Class II or III, EKG evidence of LVEF <45%, in sinus rhythm, on stable doses of diuretics, capable of 3-12 minutes of exercise.
Packer 1986 US Single center Open (Poor)	21 Captopril 21 Enalapril	A: Captopril 50 mg TID. B: Enalapril 20 mg BID. 12 weeks	Patients with severe HF (persistent dyspnea or fatigue at rest or during minimal exertion, despite treatment with digitalis and diuretics; LVEF <30%).
Zannad 1992 France Multicenter (Poor)	138 Lisinopril 140 Enalapril	B: Lisinopril 2.5 mg single dose, then 5 mg once daily for 2 weeks, then if needed and tolerated 5 mg once daily for 4 weeks, then 10 mg once daily if needed to 12 weeks. Dose decreased at any point if hypotension or adverse effects. A: Enalapril 2.5 mg single dose, then 5 mg once daily for 2 weeks, then if needed and tolerated 5 mg once daily for 4 weeks, then 10 mg once daily if needed to 12 weeks. Dose decreased at any point if hypotension or adverse effects. 12 weeks	Over age 21 with NYHA Class II or III, on optimal dose of digitalis and/or diuretics and capable of 4-12 minutes of exercise protocol; underlying cause of HF not used to judge eligibility.

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Baseline NYHA Class
Morisco 1997 Italy Multicenter (Fair)	Loop diuretics, long-acting nitrates, amiodarone, anticoagulants allowed. Treatment with potassium-sparing agents, digitalis glycosides, calcium-channel blockers, beta-blockers, vasodilators, all antihypertensive medications withdrawn.	Physical exam and symptom review at recruitment and at each visit. Exercise test (bicycle) at 6 and 12 weeks and baseline.	Lisinopril vs Captopril: Mean age 69 (sd0.5) vs 70 (sd 0.5) 80% vs 75% males Ethnicity NR	Lisinopril vs Captopril: Class II: 70% vs 74% Class III: 30% vs 26%
Packer 1986 US Single center Open (Poor)	Maintenance treatment with oral digitalis, diuretics kept constant, salt-restricted diet continued, previously prescribed vasodilators discontinued, no maintainance treatment with oral potassium supplements, potassium-sparing diuretics, or direct-acting vasodilators	Not clear- discussion of hemodynamics, but not clinical assessment.	Captopril vs Enalapril Mean age 59 (sd 2.9) vs 62.2 (sd 3.0) 90% vs 76% males Ethnicity NR	Baseline NYHA class NR; Cause of heart failure, Captopril vs Enalapril: Ischemic heart disease 57% vs 71% Primary dilated cardiomyopathy 29% vs 29% Primary valvular disease 14% vs 29%
Zannad 1992 France Multicenter (Poor)	Before randomization, 10-14 day placebo period in which digoxin and/or diuretic doses optimized, all other vasodialator and ACE Inhibitor treatment withdrawn. Digoxin and/or diuretics maintained throughout study, potassium supplements reported if hypokalemia developed. No potassium-sparing diuretics, nitroglyerin permitted, anticoagulant treatment permitted.	Exercise test at baseline, 6 and 12 weeks, Holter monitor at baseline and week 12, blood chemistry at entry, 2,4,6,12 weeks; adverse events volunteered at each visit.	Lisinopril vs Enalapril mean age 63 (sd 10, range 26-84) vs 61 (sd 10, range 28-80) 86% vs 81% male Ethnicity NR	Lisinopril vs Enalapril: Class II: 58% vs 64% Class III: 42% vs 36%

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed	Results	Adverse Effects Reported
Morisco 1997 Italy Multicenter (Fair)	# screened NR 271 eligible 251 enrolled	37 withdrawn 0 lost to followup 214 analyzed	NYHA Class, Lisinopril vs Captopril 37.8% vs 36.9% improved 61.2% vs 60.2% no change 1% vs 2.9% deteriorated changes similar in both groups (no p-values reported). Improvement in signs and symptoms similar (third heart sounds, jugular venous distension, rales, edema, orthopnea, dyspnea)	Volunteered adverse effects obtained at each visit. Captopril: 20 patients withdrew, 5 for adverse effects, Lisinopril: 17 withdrew, 8 for adverse effects (p=NS) 2 Captopril, 0 Lisinopril died 11.4% of Captopril vs 14.1% of Lisinopril had adverse effects not leading to withdrawal Adverse effects leading to withdrawal, Captopril vs Lisinopril hypotension 1 vs 2, hypertension 1 vs 0, fatigue 1 vs 0, rash, pruritis 1 vs 1, vomiting 1 vs 0, icterus 0 vs 1, abdominal pain 0 vs 1, dyspnea 0 vs 1, renal dysfunction 0 vs 2.
Packer 1986 US Single center Open (Poor)	# screened NR # eligible NR 42 enrolled	0 withdrawn 0 lost to followup 42 analyzed	Improvement by at least 1 NYHA class: Captopril 71% vs Enalapril 52 % Captopril: 29% did not benefit clinically (1 died suddenly of ventricular tachycardia) vs Enalapril: 48% did not benefit clinically (1 died of GI bleeding)	Captopril: 10 patients episodic dizziness (1 syncope), 1 patient rash, 1 patient dysguesia, 5 patients increase in blood urea nitrogen (azotemia) Enalapril: 11 patients episodic dizziness (6 had syncope or near syncope), worsening azotemia in 9 patients; 2 patients symptomatic hypotension after 1st dose, 1 patient severe dizziness and chest pain4 hours after 1st dose; 1 patient developed severe symptomatic hypotension after 6 weeks of Enalapril.
Zannad 1992 France Multicenter (Poor)	# screened NR 300 eligible NR 278 enrolled	29 withdrawn # lost to followup NR 249 analyzed	Lisinopril vs Enalapril: NYHA Class at 12 weeks: 48% improvement vs 43% improvement 49% no change vs 53% no change 3% deterioration vs 2% deterioration (All p= NS) Symptoms: Both drugs improved monitored symptoms, and effects of treatment similar for groups Mean increase in exercise duration at 6 weeks: 30.1 sec vs 13.5 sec (p=0.1415) Mean increase in exercise duration at 12 weeks: 65.1 sec vs 41.9 sec (p=0.0748)	No significant differences with respect to incidence of spontaneously reported symptoms, side effects, or withdrawals from treatment.

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number	Interventions (drug, regimen, duration)	Eligibility criteria
Zannad 1998 France (Fair)	122 Fosinopril 132 Enalapril	A: Fosinopril 5 mg once daily for 2 weeks, then 10 mg once daily for 4 weeks, then 20 mg once daily for up to 12 months (all if no decrease in BP) B: Enalapril 5 mg once daily for 2 weeks, then 10 mg once daily for 4 weeks, then 20 mg once daily for up to 12 months (all if no decrease in BP). 12 months	Ages 18-85, stratified to include at least 1/3 over age 65, NYHA Class II or III and LVEF <40% ; receiving diuretics.
Zebrah Study Group (Adgey) 1993 UK Multicenter (Fair)	127 Lisinopril 124 Enalapril	A: Lisinopril 5 mg once daily, increased to 10 mg then 20 mg if SBP >90, no symptoms of hypotension and no clinical reason not to increase the dose. B: Enalapril 5 mg once daily, increased to 10 mg then 20 mg if SBP >90, no symptoms of hypotension and no clinical reason not to increase the dose. 6 months	Over age 18 with NYHA Class III or IV confirmed by clinical signs or symptoms and LVEF <35%, capable of at least 1 minute of exercise test and in sinus rhythm or controlled atrial fibrillation.

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Baseline NYHA Class
Zannad 1998 France (Fair)	Diuretics, diltiazem, nitrates, digitalis allowed.	Rate of death and hospitalization for worsening HF, time to first critical event (event-free survival time), change in NYHA class, cardiac symptoms and signs; 12 months of followup.	Fosinopril vs Enalapril: Mean age 63.3 (sd 9.2, range 35-79) vs 63.6 (sd 10.7, range 23-70) 81% vs 75% male Ethnicity NR	Fosinopril vs Enalapril: Class II: 84% vs 80% Class III: 16% vs 20%
Zebrah Study Group (Adgey) 1993 UK Multicenter (Fair)	Current diuretic and/or digoxin treatment optimized and kept constant 2 weeks before treatment. Concurrent treatment with anti-coagulants, anti-arrhythmics, or vasodilator drugs permitted but had to remain constant during the study or patient was withdrawn. Occasional sublingual GTN, taken as required, was permitted. Medication for conditions other than Heart f was recorded and kept constant if possible.	Exercise stress test at visit 1, at visit 2, baseline exercise test, LVEF measured, NYHA Class recorded, abbreviated symptom review and physical exam. At subsequent visits (timing not clear), adverse events, abbreviated symptom review, physical exam. Final visit at 6 months: all measurements, exercise test, NYHA class, LVEF, chest x-ray.	Lisinopril vs Enalapril: Mean age 62.4 vs 62.9 79% vs 82% male Ethnicity NR	Lisinopril vs Enalapril: Class III: 80% vs 82% Class IV: 20% vs 18%

Evidence Table 9. Head-to-head trials of ACE-Inhibitors for heart failure

Author Setting (Quality)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed	Results	Adverse Effects Reported
Zannad 1998 France (Fair)	296 screened 280 eligible 254 enrolled	94 withdrawn # lost to followup NR 254 analyzed	Fosinopril vs Enalapril: Death 1.6% vs 4.6% Withdrawal for worsening HF 4.9% vs 7.6% Hospitalization for worsening HF 0.8% vs 3.0% Supplementary frusomide or emergency department for worsening HF 4.9% vs 5.3% None of the above 12.2% vs 20.5% (p=0.059) Total hospitalization and death 19% vs 25% (p=0.28) Event-free survival time 1.6 vs 1.0 months (p=0.032)	
Zebrah Study Group (Adgey) 1993 UK Multicenter (Fair)	# screened NR # eligible NR 251 enrolled	68 withdrawn # lost to followup NR 194 analyzed	Lisinopril vs Enalapril: NYHA Class at 6 months: Class I: 8% vs 6% Class II: 51% vs 59% Class III: 38% vs 32% Class IV: 3% vs 2% Improvement by one or more class: 68% vs 70% (p=NS)	Lisinopril vs Enalapril Most common adverse effects: Dizziness 37 vs 45 Cough 15 vs 18 Dry cough 13 vs 15 Headache 7 vs 19 Tiredness 8 vs 12 Diarrhea 11 vs 6 Nausea 6 vs 8 Syncope 5 vs 7 Confusion 3 vs 7

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline?	Similarity to target population
Acanfora 1997 Italy	Fair	Quinapril vs Captopril	Method not described	NR	Yes	Similar
Bach 1992 Germany, Italy	Poor	Lisinopril vs Captopril	Computer-generated	NR	Yes	Similar
Beynon 1997	Poor	Captopril vs Quinapril	Method not described	No, open	Yes	Similar, although single center
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	Fair	Cilazapril vs Captopril	Method not described	NR	Cilazapril lower score on 2 measures at baseline, no statistical test reported.	Similar

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Acanfora 1997 Italy	MI or revascularization surgery in previous 3 months; angina at rest or intermittent cladication; CV events in previous 6 months, chronic bronchopulmonary disease, atrial fibrillation or severe arrhythmias, fixed heart pacemakers, hemodynamically significant aortic or mitralic stenosis, significant renal or hepatic failure, hemopoietic or endocrine diseases; SBP 90 or lower or 190 or higher, hypersensitivity or other contraindicatio nof ACE inhibitors, potassium < 3 or >5.5, receiving treatment with potassium-sparing diuretics, positive inotropic drugs (except digoxin), allopurinol, cytostatic, immunosuppressants, beta-blockers, calcium antagonists, vasodilators, other ACE inhibitors.	Yes	Yes	NR	Yes
Bach 1992 Germany, Italy	Recent history of MI or cardiac surgery, cerebrovascular accident, clinically important renal disorders, right heart failure, lung disease limiting exercise tolerance, drug or alcohol abuse.	Yes	Yes	NR	Yes
Beynon 1997	Acute HF or rapidly deteriorating status, hepatic or renal dysfunction, MI within 6 weeks, unstable angina, or other disease precluding survival, etc, p 585 table.	Yes	No	NR	No
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	Myocardial infarction or stroke within previous 3 months, surgery for primary valvar disease, a pacemaker, or systolic blood pressure <90 mm Hg.	Yes	Yes	NR	Yes

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
Acanfora 1997 Italy	Not clear; states "complete data were available for 131 patients."	Yes	Yes	2 dropped due to adverse effects, both Captopril, 0 Quinapril.	NR	Yes	12 weeks
Bach 1992 Germany, Italy	No- completers analysis and per protocol analysis	84% (125/148) lisinopril vs 91% (127/139) captopril completed	Yes	Yes- more lisinopril withdrew, high withdrawal. 315 entered, 28 withdrew at runin, 38 withdrew during treatment (total 66/315=21%)	NR	Yes	12 weeks
Beynon 1997	Yes, but Table IV is not ITT, check text and report results of ITT	Not sure	Yes	Yes- 48% of captopril avs 37% of quinapril withdrew	Supported by grant from Parke Davis	Yes	16 weeks after 2 to 8 weeks titration
Bulpitt et al. 1998 Multicenter UK, Germany, Switzerland	No- only analyze results on patients with complete data	Not sure	Attrition yes, others no.	18% with no followup data- not reported by group	Supported by grant from Hoffmann-LaRoche, Switzerland	Yes	24 weeks

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline?	Similarity to target population
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	Fair	Cilazapril vs Captopril	Method not described	NR	Yes	Similar
de Graeff 1989 Tbe Netherlands	Poor	Ramipril vs Captopril	Method not described	No, open	7 ramipril, 6 captopril patients-appear similar, no statistical tests reported	Similar
Dirksen 1991	Poor	Enalapril vs Captopril	Method not described	No, open	Yes	Similar
Gavazzi 1994 Italy	Fair	Quinapril vs. Captopril	Method not described	NR	Higher prevalence of NYHA Class II in quinapril ($p<0.05$), otherwise yes	Similar

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	MI or cerebral stroke in past 3 months, surgery for primary valvular disease or pacemaker implantation indicated, systolic blood pressure <90 mm Hg or other clinically significant disease.	Yes	Yes	NR	Yes
de Graeff 1989 Tbe Netherlands	Acute myocardial infarction or unstable angina pectoris within the preceding 6 weeks, SBP 90 or less, severe valvular disease and creatinin clearance less than 30ml/min.	Yes	No	NR	No
Dirksen 1991	Hypotension (SBP <60), acute HF or MI within 2 months, cerebrovascular accident within 6 months	Yes	No	NR	No
Gavazzi 1994 Italy	After washout, if systolic BP <110 or diastolic BP <70, creatinine concentration 221 or more.	Yes	Yes, not for washout	not clear	Yes

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
Cilazapril-Captopril Multicenter Group, 1995 Multiple centers in Western Europe, Australia, Canada	Unable to determine.	Unable to determine	Attrition yes, others no.	Not reported	NR; authors who prepared and analyzed data were from Hoffmann-LaRoche.	Yes	24 weeks
de Graeff 1989 Tbe Netherlands	individual results reported	Yes	Yes	only 8/12 completed (67%)	NR	Yes	12 weeks
Dirksen 1991	Those withdrawing at run-in not evaluated	Yes	Yes	12/52 (23%) withdrawn at run-in, not reported breakdown by drug- 19 enalapril and 21 captopril received treatment	Not reported	No	12 weeks
Gavazzi 1994 Italy	Yes	yes?	yes	11.4% of Captopril and 10.5% of Quinapril withdrew	supported by grant from Parke-Davis	Yes	12 weeks

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline?	Similarity to target population
Giles 1988, 1989 US	Fair	Lisinopril vs Captopril	Method not described	NR	Yes	Excluded those with history of captopril intolerance
Haffner 1995 UK	Poor	Captopril vs Enalapril	No	NR	Yes	No? Withdrawn if poor compliance, decreased cardiac function, severe adverse effects, death.
Morisco 1997	Fair	Lisinopril vs captopril	Method not described	NR	Yes	Yes, but limited to elderly patients
Packer 1986 US	Poor	Captopril vs Enalapril	Computer-generated	not described	Yes	Patients with severe HF, persistent symptoms despite digitalis and diuretics

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Giles 1988, 1989 US	History of captopril intolerance, recent unstable angina, MI, or cerebrovascular accident, clinically important renal, hepatic, or hematologic disorders, hyper- or hypokalemia cor pulmonale, aortic valvular heart disease, sytolic BP < 80, substance abuse.	Yes	Yes	NR	Yes
Haffner 1995 UK	SBP >190 or <110; serum creatinine >300, clinical signs of aortic or mitral stenosis or cor pulmonale.	Yes	Yes	NR	Yes
Morisco 1997	MI or cardiac surgery (including PTCA) in last 3 months, stable or unstable angina, cerebrovascular accident in previous 6 months, intermittent claudicaiton, right heart failure, severe pulmonary disease limiting exercise performance, atrial fibrillation, arryhtmias requiring treatment other than amiodarone, fixed rate prcemakers, significant aortic or mitral valve stenosis or regurgitation, clinically relevant renal, hepatic, endocrine, or hematological disorders SBP <90 or >160, history of ACE inhibitor intolerance, hyper- or hypokalemia, receiving other investigational treatment, alcohol abuse.	Yes	Yes	NR	Yes, double dummy
Packer 1986 US	NR	yes	No	NR	No

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
Giles 1988, 1989 US	Yes, but not for subgroup of those over age 65.	Final doses- lisinopril vs captopril: low 35% vs 21%, medium 27% vs 29%, high 38% vs 50%	Yes	11% in each group withdrew due to adverse effects	Supported in part by Merck Sharp and Dohme, some investigators from Merck Sharp and Dohme	Yes	12 weeks
Haffner 1995 UK	No	Not sure	yes	High loss- 96 entered, 16 ineligible at run-in (17%), 24 more withdrawn (total loss=42%: 40/96); 30 withdrew after randomization	Supported by Bristol-Myers Squibb	Yes	6 months
Morisco 1997	Yes	Dose at end: lisinopril vs captopril: 48.5% vs 50.4% low, 27% vs 25.4% medium, 24% vs 24.2% high	Yes	20/271 withdrew at run-in (7%); 20/123 (16.3% of captopril nd 17/128 lisinopril (13.2%) withdrew	NR	Yes	12 weeks
Packer 1986 US	Yes?	Yes	Yes	No	Supported by NIH/NHLBI	No, not titrated (for either group)	12 weeks

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Score (good/ fair/ poor)	Comparison	Random assignment	Allocation concealed	Groups similar at baseline?	Similarity to target population
Zannad 1992 France	Poor	Lisinopril vs Enalapril	Method not described	NR	Mean exercise capacity at end of run-in lisinopril vs enalapril: 433 (sd 119) vs 462 (sd 141) (p=NS); significant difference before run-in	Similar
Zannad 1998 France	Fair	Fosinopril vs Enalapril	Method not described	NR	Yes	Similar
ZEBRAH (Adgey) 1993	Fair	Lisinopril vs Enalapril	Method not described	NR	Yes	Similar- withdrawn if first-dose hypotension.

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Zannad 1992 France	Recent history of MI or cardiac surgery, or clinically important renal disease, lung disease, angina limiting exercise capacity, arrhythmias requiring treatment other than digoxin or amiodarone, known sensitivity or contraindication to ACE inhibitors.	Yes	Yes	NR	Yes
Zannad 1998 France	Symptoms of unstable angina in past 1 month, MI past 3 months, obstructive cardiac valvular disease and cardiomyopathy, BP < 90, severe liver disase, renal dysfunction.	Yes	Yes	NR	Yes
ZEBRAH (Adgey) 1993	MI, cardiac surgery or PTCA in previous 3 months, unstable angina or severe angina limiting exercise, CVA in past 6 months, right heart failure due to lung disease, lung disease limting exercise performance, uncontrolled arrhythmias, hemodynamically significant aortic stenosis. Clinically relevant renal diseae or serum creatinine >150, clinically significant hemopoietic or endocrine disorders (except controlled diabetes mellitus), bilateral renal artery stenosis, constrictive pericarditis or SBP <80, known hypersensitivity or contraindication to ACE inhibitors, or recent history of drug or alcohol abuse or poor compliance; women of childbearing potential.	Yes	Yes	NR	Yes

NR = Not Reported

Evidence Table 10. Quality assessment head-to-head trials of ACEIs for heart failure

Study Setting	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Funding	Control group standard of care?	Length of follow-up
Zannad 1992 France	No- 'completers analysis'	Yes	Yes	22/200 withdrew at run-in (7%), 29 during treatment (total 17% withdrawal) 15 enalapril and 14 lisinopril withdrew, # randomized in each group not given	NR	No	12 weeks
Zannad 1998 France	Yes	?	Yes	23% of fosinopril and 26.5% of enalapril discontinued due to adverse effects, including worsening heart failure	Sponsored by Bristol-Myers-Squibb as part of development plan for fosinopril	Yes	12 months
ZEBRAH (Adgey) 1993	No	?	Yes	High overall loss: 30/127 (24%) Lisinopril 30/124 (24%) Enalapril	Zeneca provided financial and logistical support.	Yes	6 months

NR = Not Reported

Evidence Table 11. Results of systematic review of placebo-controlled trials of ACEIs for heart failure (From Garg 1995)

Intervention	Study	Number of Patients	Total Mortality (Odds Ratio)	95% CI	Mortality or Hospitalization (Odds Ratio)	95% CI
Benazepril	Colfer et al.	172	0.05	0-0.55	0.22	0.04-1.22
	McGarry	61	2.21	0.22-22.15	0.90	0.25-3.31
	Summary	**233**	**0.36**	**0.07-1.90**	**0.54**	**0.19-1.52**
Captopril	Magnani	494	1.14	0.35-3.64	--	--
	Bussman	23	0.55	0.08-3.83	--	--
	Captopril Digoxin Multicenter	204	1.18	0.56-2.49	0.82	0.45-1.50
	CMRG	105	0.20	0.06-0.65	0.19	0.06-0.59
	Barabino	101	0.52	0.22-1.22	0.32	0.14-0.70
	Kleber	170	1.07	0.54-2.11	0.94	0.51-1.72
	Summary	**697**	**0.79**	**0.54-1.14**	**0.61**	**0.43-0.87**
Cilazapril	Drexler	21	0.12	0-6.20	0.89	0.11-7.51
	Summary	**21**	**0.12**	**0-6.20**	**0.89**	**0.11-7.51**
Enalapril	Cleland	20	(0 deaths)			
	Rucinska	132	0.48	0.09-2.48	0.48	0.09-2.48
	CONSENSUS	253	0.56	0.34-0.91	0.89	0.51-1.57
	Enalapril CHF Investigators	256	0.57	0.19-1.66	0.51	0.18-1.45
	Dickstein	41	0.14	0-7.16	0.12	0.02-0.93
	SOLVD	2569	0.82	0.70-0.97	0.68	0.59-0.80
	Rucinska	110	0.14	0-6.82	0.14	0.00-6.82
	Summary	**3381**	**0.78**	**0.67-0.91**	**0.68**	**0.59-0.79**
Lisinopril	Zwehl	275	0.83	0.19-3.67	0.83	0.19-3.67
	Giles	193	0.34	0.08-1.40	0.27	0.07-1.05
	Rucinska	58	7.94	0.16-400.92	1.07	0.07-17.61
	Gilbert	20	(no deaths)			
	Summary	**546**	**0.62**	**0.23-1.67**	**0.50**	**0.19-1.27**
Perindopril	Lechat	125	0.14	0-7.16	0.14	0.01-2.26
	Summary	**125**	**0.14**	**0-7.16**	**0.14**	**0.01-2.26**
Quinapril	Riegger	225	(no deaths)	--	--	--
	Northridge	32	(no deaths)	--	--	--
	Uprichard	224	0.49	0.05-4.78	0.49	0.05-4.78
	Uprichard	208	0.65	0.11-3.83	0.65	0.11-3.83
	Uprichard	186	3.84	0.16-94.01	3.84	0.16-94.01
	Summary	**875**	**0.79**	**0.22-2.85**	**0.79**	**0.22-2.85**
Ramipril	Swedberg	223	0.41	0.11-1.44	0.42	0.17-1.01
	Maass	132	1.40	0.30-3.61	1.04	0.30-3.61
	Gordon	192	0.27	0.05-1.34	0.25	0.08-0.81
	Maass	500	0.82	0.26-2.63	0.58	0.25-1.38
	Maass	95	1.02	0.06-16.58	0.67	0.11-4.04
	Lemarie	85	7.57	0.15-381.49	0.75	0.16-3.51
	Summary	**1227**	**0.67**	**0.36-1.24**	**0.52**	**0.33-0.83**
All ACE Inhibitors	**Summary**		**0.77**	**0.67-0.88**	**0.65**	**0.57-0.74**

Evidence Table 12. Adverse effects reported in head-to-head trials of placebo-controlled trials of ACE Inhibitors for recent myocardial infarction

Study Year	Interventions	Significant hypotension	Cough	Angioedema	Significant renal failure	Overall withdrawals	Withdrawal due to adverse events
Head-to-head trials of one included ACEI vs. another included ACEI							
Foy 1994	A: Captopril B: Enalapril	NR	8% 5%	NR	NR	24% 16%	Not clear
Lau 2002	A: Captopril B: Perindopril	7% 2%	5% 3%	NR	NR	14% 9%	NR
Trials of an included ACEI vs. placebo							
Trials of Captopril vs. placebo							
ISIS-4 1995	A: Captopril B: Placebo	10% 5%	NR	NR	1.1% 0.6%	NR	NR
Kingma (CATS) 1994	A: Captopril B: Placebo	27% 18%	NR	NR	NR	NR	NR
Kleber (ECCE) 1997	A: Captopril B: Placebo	37% 18%	NR	NR	NR	4% 12%	Not clear ('severe' adverse events 17% vs. 17%)
Kober (TRACE) 1995	A: Captopril B: Placebo	31% 22%	34% 21%	NR	14% 11%	37% 36%	Not clear
CCS-1 1997	A: Captopril B: Placebo	8.0% 4.7%	5.0% 4.2%	NR	NR	NR	NR
Rutherford (SAVE) 1994	A: Captopril B: Placebo	NR	6% NR	NR	NR	NR	6% (68/1115) 3% (39/1116)
Shen 1996	A: Captopril B: Placebo	NR	NR	NR	NR	NR	NR
Trials of other ACEIs vs. placebo							
Swedberg (CONSENSUS II) 1992	A: Enalapril B: Placebo	25% 10%	NR	NR	2.4% 1.0%	18% 12%	10% (296/3044) 4.5% (138/3046)
Borghi (FAMIS) 1998	A: Fosinopril B: Placebo	10% 10%	6% 5%	NR	8% 6%	NR	NR
GISSI-3 1994	A: Lisinopril B: Placebo (open)	9% 4%	NR	NR	2.4% 1.1%	Not clear	Not clear
AIRE 1993	A: Ramipril B: Placebo	4% 2%			1.5% 1.2%	35% 32%	13% (126/1004) 7% (68/982)
Ambrosioni (SMILE) 1995	A: Zofenopril B: Placebo	17% 9%	NR	NR	NR	8.6% 6.8%	NR

Evidence Table 13. Adverse effects reported in head-to-head trials of ACE Inhibitors for heart failure

Author Year Country	N	Comparison	Overall Withdrawals	Withdrawals Due to Adverse Effects	Hypotension	Withdrawals due to Hypotension
Acanfora 1997	121	Quinapril 10-20 mg once daily Captopril 12.5-25 mg BID	0% Quinapril 3% Captopril	0% Quinapril 3% Captopril	Not reported	Not reported
Bach 1992	287	Lisinopril 5 -20 mg once daily Captopril 12.5-50 mg BID	12% overall	6% Lisinopril 5% Captopril	Not reported	Not reported
Beynon 1997	61	Captopril 6.25-50 mg BID Quinapril 2.5-20 mg BID	48% Captopril 37% Quinapril	39% Captopril 27% Quinapril	16% Captopril, 17% Quinapril 1st dose hypotension	0% captopril 3% quinapril withdrew due to 1st dose hypotension
Bulpitt	269	Cilazapril 1 mg-2.5 mg once daily Captopril 25 mg TID-50 mg TID	18% overall	Not reported	Not reported	Not reported
Cilazapril-Captopril Study Group	329	Cilazapril 1 mg-2.5 mg once daily Captopril 25 mg TID-50 mg TID	22% Cilazapril 25% Captopril	5.4% Cilazapril 13.0% Captopril	Overall not reported; 0 cilazapril vs 2 captopril experience first-dose hypotension not leading to withdrawal.	Not reported

Evidence Table 13. Adverse effects reported in head-to-head trials of ACE Inhibitors for heart failure

Author Year Country	N	Comparison	Overall Withdrawals	Withdrawals Due to Adverse Effects	Hypotension	Withdrawals due to Hypotension
de Graeff 1989	13	Ramipril 5-10 mg BID Captopril 12.5-50 mg TID	33% Captopril 14% Ramipril	14% Captopril 20% Ramipril	Captopril: 20% tolerated only 12.5 mg BID, Ramipril: 29% tolerated only 5 mg due to hypotension 29% Ramipril and 20% Captopril developed symptomatic hypotension (not serious enough to withdraw)	0
Dirksen 1991	40	Enalapril 10-20 mg once daily Captopril 12.5-25 mg TID	Not Clear	11% Enalapril 19% Captopril	0	0
Gavazzi 1994	146	Quinapril 10-20 mg once daily Captopril 25-50 mg BID	11% Captopril 11% Quinapril	7% Quinapril 9% Captopril	4% Captopril, 3% Quinapril had hypotension. 1% captopril, 3% quinapril had 1st dose or orthostatic hypotension. At week 4 increase in dose, 4% captopril, 1% quinapril had hypotension or orthostatic hypotension.	1% captopril withdrew at week 4 after hypotension due to dose increase.
Giles 1988, 1989	65	Lisinopril 5-20 mg once daily Captopril 12.5-50 mg TID	Not reported	2% Lisinopril 2% Captopril	0% lisinopril, 2% captopril hypotension. Symptomatic hypotension in 2% of captopril Subgroup of patients over age 65: 0% lisinopril and 4% captopril had serious hypotension	2% lisinopril discontinued due to mild, nonserious hypotension.
Haffner 1995	80	Captopril 12.5 mg BID Enalpril 2.5 mg BID	24 patients withdrew *Total events:* 13 Captopril 14 Enalapril	9 events Captopril 10 events Enalapril	Not reported	0% captopril and 10% enalapril withdrew due to symptomatic hypotension.

Evidence Table 13. Adverse effects reported in head-to-head trials of ACE Inhibitors for heart failure

Author Year Country	N	Comparison	Overall Withdrawals	Withdrawals Due to Adverse Effects	Hypotension	Withdrawals due to Hypotension
Morisco 1997	251	Lisinopril 5-20 mg once daily Captopril 12.5-25 mg BID	16% Lisinopril 13% Captopril	4% Lisinopril 6% Captopril	Not reported	1% captopril, 2% lisinopril withdrew due to hypotension.
Packer 1986	42	Captopril 50 mg TID Enalapril 20 mg BID	0	None	0% captopril, 10% enalapril had 1st dose symptomatic hypotension. 5% enalapril serious hypotension after 6 weeks of treatment.	0
Zannad 1992	278	Lisinopril 5-10 mg once daily Enalapril 5-10 mg once daily	10% Lisinopril 11% Enalapril	9% Lisinopril 6% Enalapril	Not reported	1 lisinopril, 2 enalapril
Zannad 1998	254	Fosinopril 5-20 mg once daily Enalapril 5-20 mg once daily	37% Fosinopril 36% Enalapril	3% Fosinopril 3% Enalapril	All hypotension: 4.9% fosinopril, 4.5% enalapril Symptomatic orthostatic hypotension: 1.6% fosinopril, 7.6% enalapril ($p<0.05$)	Not reported
Zebrah Study Group (Adgey) 1993	251	Lisinopril 5-20 mg once daily Enalapril 5-20 mg once daily	24% Lisinopril 31% Enalapril	20% Lisinopril 21% Enalapril	1st dose hypotension: 0% lisinopril, 1% enalapril. Hypotension, 2% lisinopril, 1% enalapril	Not reported

Appendix A. Search strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2005>
Search Strategy:
---

1 quinapril.mp.
2 benazepril.mp.
3 moexipril.mp.
4 captopril.mp.
5 enalapril.mp.
6 lisinopril.mp.
7 ramipril.mp.
8 fosinopril.mp.
9 perindopril.mp.
10 trandolapril.mp.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 congestive heart failure.mp. or Heart Failure, Congestive/
13 (Hypertens$ or high blood pressure).mp.
14 diabetes mellitus.mp. or Diabetes Mellitus/
15 myocardial infarct$.mp. or Myocardial Infarction/
16 12 or 13 or 14 or 15
17 11 and 16
18 limit 17 to yr=1998 - 2004
19 limit 17 to yr=1992 - 1997
20 limit 17 to yr=1898 - 1991
21 from 20 keep 1-1179

Database: Ovid MEDLINE(R) <1996 to February Week 3 2005>
Search Strategy:
---

1 quinapril.mp.
2 benazepril.mp.
3 moexipril.mp.
4 captopril.mp.
5 enalapril.mp.
6 lisinopril.mp.
7 ramipril.mp.
8 fosinopril.mp.
9 perindopril.mp.
10 trandolapril.mp.
11 cilazapril.mp.
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 congestive heart failure.mp. or exp Heart Failure, Congestive/
14 Hypertension/ or high blood pressure.mp.

15 diabetes mellitus.mp. or exp Diabetes Mellitus/
16 myocardial infarct$.mp. or exp Myocardial Infarction/
17 exp kidney diseases/ or nephropath$.mp.
18 13 or 14 or 15 or 16 or 17
19 12 and 18
20 limit 19 to (controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial)
21 exp Randomized Controlled Trials/ or rct.mp.
22 systematic review$.mp.
23 21 or 22
24 19 and 23
25 20 or 24
26 limit 25 to (human and english language)
27 limit 26 to (adult <19 to 44 years> or middle age <45 to 64 years> or "all aged <65 and over>" or "aged <80 and over>")
28 (200402$ or 200403$ or 200404$ or 200405$ or 200406$ or 200407$ or 200408$ or 200409$ or 20041$ or 2005$).ed.
29 27 and 28
30 from 29 keep 1-120

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 24, 2005>
Search Strategy:
---
1 quinapril.mp.
2 benazepril.mp.
3 moexipril.mp.
4 captopril.mp.
5 enalapril.mp.
6 lisinopril.mp.
7 ramipril.mp.
8 fosinopril.mp.
9 perindopril.mp.
10 trandolapril.mp.
11 cilazapril.mp. [mp=title, abstract]
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 (congestive heart failure or chf).mp.
14 (Hypertens$ or high blood pressure).mp.
15 diabetes mellitus.mp.
16 (myocardial infarct$ or heart attack$).mp.
17 nephropath$.mp.
18 13 or 14 or 15 or 16 or 17
19 12 and 18
20 from 19 keep 1-136

Database: EMBASE Drugs & Pharmacology <1991 to 1st Quarter 2005>
Search Strategy:
---

1 quinapril.mp.
2 benazepril.mp.
3 moexipril.mp.
4 captopril.mp.
5 enalapril.mp.
6 lisinopril.mp.
7 ramipril.mp.
8 fosinopril.mp.
9 perindopril.mp.
10 trandolapril.mp.
11 cilazapril.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 congestive heart failure.mp. or exp Congestive Heart Failure/
14 Hypertension/ or high blood pressure.mp.
15 diabetes mellitus.mp. or exp Diabetes Mellitus/
16 myocardial infarct$.mp. or exp Myocardial Infarction/
17 exp kidney diseases/ or nephropath$.mp.
18 13 or 14 or 15 or 16 or 17
19 12 and 18
20 exp Randomized Controlled Trials/ or randomized controlled trial$.mp. or rct.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
21 systematic review$.mp.
22 practice guideline.mp. or exp Practice Guideline/
23 meta-analysis.mp. or exp meta analysis/
24 multicenter study.mp. or exp multicenter study/
25 controlled clinical trial$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
26 21 or 22 or 23 or 24 or 25
27 19 and 26
28 limit 27 to (human and english language)
29 limit 28 to (adult <18 to 64 years> or aged <65+ years>)
30 ("200300" or "200401" or "200501").em.
31 29 and 30
32 from 31 keep 1-38

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

<u>Assessment of Internal Validity</u>

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making,

i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.