

# **Drug Class Review On Angiotensin Converting Enzyme Inhibitors**

**Executive Summary**  
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## OVERVIEW

Angiotensin-converting-enzyme-inhibitors (ACEIs) block the activation of the renin-aldosterone system, an important mediator of blood pressure. In addition to reducing blood pressure, ACEIs are also thought to improve ventricular remodeling following myocardial infarction, reduce mortality in patients with heart failure, and prevent 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, in patients with systolic heart failure, and in patients at high risk for cardiovascular events. In addition, the American Diabetes Association recommends ACEIs as standard treatment for patients with diabetic nephropathy. Ten ACEIs are currently marketed in the US: benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

The role of ACEIs in treating patients who have high blood pressure is evolving. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (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.

## Key Questions

The key questions for this review were:

1. For adult patients with essential hypertension, heart failure, high cardiovascular risk factors, diabetic nephropathy, non-diabetic 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, non-diabetic 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?

These questions, and the eligibility criteria for this systematic review, were developed and refined with input from a subcommittee comprised of local experts

(pharmacists, primary care clinicians, neurologists, psychiatrists, and representatives of the public).

## METHODOLOGY

To identify articles relevant to each key question, we searched (in this order): the Evidence-Based Medicine Library (2003, Issue 1) (from the Cochrane Collaboration), MEDLINE (1966-May 2003), EMBASE (1980-1<sup>st</sup> Quarter 2003), 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, the State of Oregon created and disseminated a protocol (<http://www.ohppr.state.or.us/index.htm>) to pharmaceutical manufacturers for submitting dossiers, including citations, to the Evidence-Based Practice Center. All citations were imported into an electronic database (EndNote 6.0). Searches on the electronic databases were carried out through April 2003, using updates on electronic databases after the initial searches.

## FINDINGS

### Comparative Effectiveness and Adverse Effects

**Hypertension Without Compelling Indications.** A recent, comprehensive meta-analysis identified 42 controlled trials of anti-hypertension drugs reporting major cardiovascular disease end points and all-cause mortality. Nine trials involved an ACEI. None of these trials was designed to compare one ACEI to another. 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.

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) versus enalapril (5 to 20 mg twice a day), but patients assigned to captopril had better 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. 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.

No other outcomes were assessed in head-to-head trials.

**Hypertension With Compelling Indications.** In two trials (ABCD and FACET), 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 a substudy of the UKPDS, 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. 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%).

ACEIs reduce the risk of end-stage renal disease in nondiabetic patients who have renal disease (0.69 (CI, 0.51 to 0.94). Ramipril reduced the incidence of end-stage renal disease and doubling of serum creatinine in patients who had proteinuria from nondiabetic kidney diseases. Similarly, 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. Only 21% of the subjects had diabetic nephropathy, but the effect was stronger in this subgroup than in the sample as a whole.

The AASK trial compared an ACEI, a beta blocker, and a calcium channel blocker in black patients with hypertensive kidney damage. 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.

There were no important differences in the rates of cough, angioedema, hyperkalemia, or acute renal impairment in hypertension trials.

**High Cardiovascular Risk.** There are no head-to-head trials. Five placebo-controlled trials of ACEIs enrolled patients who have coronary artery disease or risk factors for cardiovascular disease but not hypertension. PROGRESS 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.

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 that has been proven to reduce all-cause mortality (NNT 56). Ramipril and enalapril reduced major cardiovascular events in patients with CAD.

In HOPE, ramipril reduced major cardiovascular events and all-cause mortality overall and in diabetics, non-diabetics, hypertensive patients, and non-hypertensive patients, but not in patients who had no history of cardiovascular disease. Perindopril reduced CV events but not all-cause mortality in EUROPA, a large placebo controlled trial.

QUIET, an angiographic study that followed patients for 2 years, had low power to detect a difference in cardiovascular events (n=1,750). In the SCAT (enalapril) and PART2 (ramipril) trials, similar proportions of patients in the placebo group had major cardiovascular events. In SCAT there was a statistically significant reduction in these events.

**Post-myocardial Infarction.** All-cause mortality and other outcomes were evaluated in two fair-quality head-to-head trials. In one mortality was 12% (9/75) on captopril versus 1.3% (1/75) on enalapril after 90 days (p=0.038), and 13% (10/75) versus 3% (2/75) (p=0.022) after 12 months. In the other, mortality was 13% (13/102) on captopril versus 6% (7/110) on perindopril after 6 months (p=0.12), with no differences in the revascularization rate (21% vs. 20%). Neither head-to-head trial reported rates of symptomatic heart failure as an endpoint.

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.

Two fair-quality systematic reviews summarized 18 trials to assess the effects of ACEIs on mortality following myocardial infarction, but were not designed to assess comparative efficacy. In good-quality placebo-controlled trials, captopril, lisinopril, ramipril, and trandolapril reduced mortality. In CONSENSUS-2 placebo was better than enalapril. Fosinopril (FAMIS) had a mixed result.

Adverse event assessment quality was generally worse than quality for assessing clinical efficacy. Reliable conclusions about differential safety or adverse event rates could not be drawn from head-to-head trials.

**Heart Failure.** One fair-quality trial showed no difference in total mortality between fosinopril and enalapril. Decreased hospitalization plus mortality in the fosinopril group may have been due to once-daily dosing of enalapril.

In 13 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 benazapril, trandolapril, moexapril, or perindopril, and no placebo-controlled trials of moexipril or trandolapril.

A fair-quality meta-analysis of 32 placebo controlled trials showed no difference in mortality or mortality plus hospitalization among benazapril, captopril, enalapril, lisinopril, perindopril, quinapril, and ramipril. There was a significant reduction in all-cause mortality in patients allocated to a treatment group (15.8%) compared with placebo (21.9%) (OR, 0.77; 95% CI 0.67-0.88), but no heterogeneity of effect among the ACEIs. There was no difference among the ACE inhibitors on the combined endpoint of total mortality or hospitalization in 30 trials that provided this information. Overall results were similar for cause-specific mortality and for trials with longer (>90 days) followup periods.

No fair or good quality head-to-head trial was designed to assess safety. In 13 head-to-head trials, the percentage of patients who withdrew due to adverse events ranged from none to 39%, and did not differ significantly between groups in any trial. Nine studies reported the number of withdrawals due to hypotension (first dose or not), and the percentages were low in most (0%-3%).

**Diabetic Nephropathy.** There are no 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.

Captopril reduced the incidence of advanced renal failure in the Collaborative Study Group trial. The study was well-conducted, but its results apply to a small proportion of diabetics—those with longstanding, poorly controlled Type 1 diabetes, most of whom had hypertension and significant proteinuria.

The European Microalbuminuria Captopril Study Group and the North American Microalbuminuria Study Group 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 and perindopril 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. Initially, enalapril improved urinary albumin excretion, but by 3 years there was no effect on this measure or on the development of hypertension.

While ACEIs reduce albuminuria in normotensive non-insulin dependent diabetics with microalbuminuria, they have not been shown to prevent the development of end-stage renal disease in this group.

Post-hoc analyses from SOLVD (enalapril) and from HOPE (ramipril) provide strong evidence that ACEIs delay or prevent the development of diabetes, particularly in patients who have glucose intolerance.

### **Subgroups**

No data suggest that one ACEI is better than others for demographic subgroups (age, race, gender). Although the recommended initial dose oftrandolapril is higher in black than in non-black patients, 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. A more recent meta-analysis of the effectiveness of ACEIs in heart failure found that, in diabetics and in blacks, the effect of ACEIs were similar to those in 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. In men the effect was similar in patients with symptomatic and asymptomatic LV dysfunction.

ACEIs appear to have more beneficial effects in post-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.