

# FPIN's Clinical Inquiries

## Do ACE Inhibitors Decrease Mortality in Patients with Hypertension?

*Am Fam Physician.* 2004 1;70(1):153-154.

### Searchable Question

Do angiotensin-converting enzyme (ACE) inhibitors decrease mortality in patients with hypertension?

### Evidence-Based Answer

When used to treat patients with hypertension, ACE inhibitors reduce cardiovascular and all-cause mortality as effectively as diuretics, beta blockers, and calcium channel blockers. [Strength of recommendation: A, based on meta-analyses of randomized controlled trials (RCTs) with patient-oriented outcomes]

### Evidence Summary

Because ACE inhibitors were introduced after other drugs for blood pressure control had been shown to reduce mortality, studies of ACE inhibitors in patients with hypertension generally compare ACE inhibitors with other antihypertensive agents. Three large meta-analyses recently reviewed these studies.

The first meta-analysis measured the efficacy of diuretics versus other agents by utilizing a network–meta-analysis technique that added emphasis to within-trial comparisons.<sup>1</sup> [Evidence level: 1A] The five RCTs that were reviewed compared ACE inhibitors with diuretics or beta blockers in 45,795 patients; data were not provided for beta blockers.

The second meta-analysis reviewed six RCTs and reported data that combined comparisons of ACE inhibitors with diuretics and beta blockers in 47,410 patients.<sup>2</sup> [Evidence level: 1A]

The third meta-analysis included six RCTs that compared ACE inhibitors with calcium channel blockers in 25,756 patients, as well as six RCTs that included diuretics and beta blockers in 47,430 patients.<sup>3</sup> [Evidence level: 1A]

All three meta-analyses concluded that ACE inhibitors were equivalent to other antihypertensive drugs in reducing cardiovascular and all-cause mortality (*see accompanying table*).<sup>1-3</sup>

Although no differences in mortality were noted in these meta-analyses, ACE inhibitors were significantly less effective in three out of four comparisons than other antihypertensive drugs in preventing stroke. ACE inhibitors were consistently less effective than other agents in reducing blood pressure. Some experts believe these two findings are causally related, although other mechanisms may be involved.<sup>3</sup>

## Meta-Analyses Comparing ACE Inhibitors with Other Antihypertensive Agents

<b>Outcome</b>	<b>ACE inhibitor vs. diuretic<sup>1</sup> (RR, 95% CI)</b>	<b>ACE inhibitor vs. diuretic or beta blocker<sup>2</sup> (RR, 95% CI)</b>	<b>ACE inhibitor vs. diuretic or beta blocker<sup>3</sup> (RR, 95% CI)</b>	<b>ACE inhibitor vs. calcium channel blocker<sup>3</sup> (RR, 95% CI)</b>
All-cause mortality	1.0 (0.95–1.05)	1.0 (0.94–1.06)	1.0 (0.95–1.05)	1.04 (0.98–1.10)
Total cardiovascular mortality	1.07 (0.98–1.15)	1.02 (0.94–1.11)	1.03 (0.95–1.11)	1.03 (0.94–1.13)
Stroke	1.14* (1.03–1.23)	1.10* (1.01–1.20)	1.09 (1.0–1.18)	1.12* (1.01–1.25)

ACE = angiotensin-converting enzyme; RR = relative risk; CI = confidence interval.

\*— Difference is statistically significant (more strokes with ACE inhibitor than comparator). Information from references 1 through 3.

It is interesting to note that all three meta-analyses included two high-profile RCTs. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the diuretic chlorthalidone (Thalitone) with the ACE inhibitor lisinopril (Prinivil) in 33,357 patients older than 55 years with a high cardiovascular risk profile (22 percent were smokers, 36 percent had diabetes, and 23 percent had prior myocardial infarction); results favored the diuretic.<sup>4</sup> [Evidence level: 1B]

The Second Australian National Blood Pressure (ANBP2) trial compared the diuretic hydrochlorothiazide (Hydrodiuril) with the ACE inhibitor enalapril (Vasotec) in 6,083 patients 65 to 84 years of age with a lower cardiovascular risk profile (7 percent were smokers, 7 percent had diabetes, and 8 percent had coronary heart disease); results favored the ACE inhibitor.<sup>5</sup> [Evidence level: 1B]

A detailed discussion of why the conclusions were at odds is beyond the scope of this Clinical Inquiry. Even so, the ACE inhibitors in the ALLHAT and ANBP2 trials reduced all-cause mortality and cardiovascular mortality to a similar extent as the diuretics.

### Recommendations from Others

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) strongly promotes the use of a low-dose thiazide diuretic (or the combination of a thiazide with another agent) as initial therapy in patients with hypertension unless there is a “compelling indication” to use a different medication.<sup>6</sup> According to the JNC 7, compelling indications for use of an ACE inhibitor are cardiovascular disease, heart failure, diabetes, chronic kidney disease, or prior stroke. In patients with diabetes and chronic kidney disease, the goal of therapy is to maintain blood pressure at 130/80 mm Hg or less.

### Clinical Commentary

ACE inhibitors are a valuable addition to the pharmacotherapy for hypertension. Physicians prescribing ACE inhibitors should ask their patients about a history of angioedema, follow the patients clinically for development of dry cough, and monitor serum potassium and creatinine levels.

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