Don't keep that ACE (inhibitor) up your sleeve!

Is ramipril effective for secondary prevention of cardiovascular disease and stroke?

D. Clayton Hammett, MD John C. MacFadyen, MD, FRCPC, MHPE

Heart Outcomes Prevention Evaluation (HOPE) study investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. N Engl J Med 2000;342:145-53.

Research question

Does an angiotensin-converting enzyme (ACE) inhibitor improve morbidity and mortality in patients with no evidence of left ventricular dysfunction or heart failure but at risk for cardiovascular events?

Type of article and design

Multicentre, international, prospective, double-blind, placebo-controlled trial.

Relevance to family physicians

HOPE is a fitting name for what might be one of the most important studies published at the dawn of the new millennium. If the results of this paper stand up to scrutiny, they should not only change the way we treat coronary artery disease (CAD), but also the way we think about the risk factors involved in genesis of CAD.

We are all aware of the various levels of evidence for using various classes of cardiac medications for various combinations of cardiac disease.[1,2] The multitude of cardiac medications overwhelms both patients and physicians and affects the compliance of both. This trial attempts to convince us that ACE inhibitors should probably be given earlier, prescribed more often, and continued longer than many other cardiac medications. It attempts to expand vastly the indications for ACE inhibitors to patients for whom you might previously have only considered using acetylsalicylic acid (ASA).

The study uses casefinding to determine which patients might benefit from treatment with an ACE inhibitor, ramipril. If the study's results are significant, they advocate for using ramipril for secondary prevention of cardiovascular disease and stroke. The inclusion and exclusion criteria in the following section might help you think of patients in your practice that would fit. There are probably quite a few.

Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator Michael Evans by e-mail michael.evans@utoronto.ca or by fax (416) 603-5821.

Overview of study and outcomes

This study had a two-by-two factorial design (two independent studies carried out on the same group of patients). It evaluates the effect of vitamin E and ramipril on the morbidity and mortality of patients with diabetes or evidence of vascular disease and one risk factor for heart disease but no evidence of left ventricular failure. The article reviews results of the ramipril study. The vitamin E study showed no benefit of vitamin E in reducing either primary or secondary end points.[3]

In the ramipril study, 9541 subjects from 267 different centres (half of them in Canada and the others in the United States, western Europe, Argentina, Brazil, and Mexico) were randomized to placebo (n = 4652), low-dose (2.5 mg) ramipril (n = 244), or 10 mg of ramipril (n = 4645). The highest dose of ramipril was titrated up to 10 mg over 4 weeks.

To be included, subjects had to be at least 55 years old, have a history of CAD, stroke, peripheral vascular disease, or diabetes mellitus, and have at least one other cardiovascular risk factor (hypertension, smoking, dyslipidemia, or microalbuminuria). Exclusion criteria were a history of congestive heart failure or evidence of an ejection fraction smaller than 40% (we already know ACE inhibitors benefit these patients), prior and ongoing treatment with ACE inhibitors or vitamin E, myocardial infarction (MI) or stroke within 4 weeks of the study, uncontrolled hypertension, or overt nephropathy. A run-in phase of 2.5 mg of ramipril daily for 7 to 10 days followed by placebo for 10 to 14 days excluded 1035 subjects before randomization due to noncompliance, withdrawal of consent, side effects, or abnormal creatinine or potassium levels.

The study's primary end point was a composite of MI, stroke, and cardiac death, each of which was also analyzed separately.

Dr Hammett *is a resident in the Department of Family and Community Medicine's rural program at the University of Toronto and works in Orillia, Ont.* **Dr MacFadyen** *is a general internist and Site Coordinator for the Rural Ontario Medical Program in Orillia and is an Assistant Professor in the Department of Medicine at the University of Ottawa.*

Table 1. **Summary of results:** *Primary end points* after treatment with 10 mg of ramipril for a mean duration of 4.4 years.*

END POINT	RAMIPRIL GROUP (N = 4645)	PLACEBO GROUP (N = 4652)	RRR (%)	ARR (%)	NNT
Myocardial infarction, stroke, or cardiac death	651	826	21	3.7	27
Myocardial infarction	459	570	19	2.4	42
Stroke	156	226	31	1.5	67
Cardiac mortality	282	377	25	2.0	49
All-cause mortality	482	569	15	1.9	54

ARR—*Absolute risk reduction,*
NNT—*Number needed to treat,*
RRR—*Relative risk reduction.*
**Subgroups are not mutually exclusive.*

Secondary end points included mortality from all causes, need for cardiac revascularization, and hospitalization for unstable angina or congestive heart failure or any complication of diabetes.

There was intention-to-treat analysis. All subjects enrolled in the study remained in the study, regardless of whether they discontinued treatment, in order to track the end points. The power of the study was set at 90% ($\alpha = 0.05$). The authors calculated that 9000 patients would be needed to detect a 13.5% relative risk reduction over 5 years.

The study was funded by the Medical Research Council of Canada, Hoechst Marion Roussel (makers of ramipril), and the manufacturers of a natural vitamin E supplement. Physicians at McMaster University coordinated the study.

Results

After a mean follow up of 4.4 years, a highly significant reduction in cardiovascular end points was seen among patients taking ramipril, so the study was stopped early. Mean age of participants was 66 years; about half were between 55 and 65 years old. About 80% had evidence of CAD, 39% had diabetes, and 47% had hypertension. Women made up 27% of the study group. Patients in each group had similar baseline characteristics. It was interesting to note that, despite their substantial risk of cardiovascular disease, only about 76% of patients were taking ASA daily. Risk reductions for primary end points are summarized in **Table 1**.

Benefit was also shown through secondary and surrogate outcome measures, the most significant of these being need for revascularization (number needed to treat [NNT] = 43), complications related to diabetes (NNT = 85), new diagnosis of diabetes (NNT = 88), and worsening angina (NNT = 42).

Many patients permanently discontinued treatment during the study: 29% of patients taking ramipril and 27% of patients in the placebo group. The most common reason for discontinuing treatment in both groups (24% in the ramipril group and 23% in the placebo group) was unspecified, but 7.3% of patients in the ramipril group discontinued due to cough.

The effect of 10 mg of ramipril on blood pressure was negligible. The benefit of 2.5 mg of ramipril appeared to be less than that of 10 mg in reducing the primary composite end point, but the number of events was small, and statistical analysis was not provided. Trends over time indicate that the benefits of ramipril probably increase beyond the duration of the study period.

Analysis of methodology

There are no apparent weaknesses in the study's randomization, methods, or analysis. The study was multinational, but about half the participants were from Canada so quite representative of patients we see in our offices. A secondary analysis was done to understand how results might have differed if all patients with low ejection fractions were excluded. Some of the surrogate outcomes will undoubtedly generate future papers.

About 28% of subjects dropped out of the study, but their end points were included in the final analysis. This is appropriate for the study design, but is one of the problems with an intention-to-treat analysis. For example, in this study, the authors did not include separate data for those who discontinued treatment, so it is impossible for us to know what percentage of the morbidity and mortality they accounted for in each group. If secondary analysis had shown that subjects who continued to take ramipril did better than those who did not, it would have added weight to their already convincing data. On the other hand, including subjects who discontinued treatment in the final results more closely approximates the effect of starting therapy in our own patients, some of whom are likely to discontinue treatment for a variety of reasons.

Presentation of results did not provide clinically useful statistics, such as the NNT or absolute risk reductions. Also, we are seldom reminded that results were derived from 4.4 years of treatment. All this makes it difficult to put these rather significant results into context. There were minor calculation errors in the outcome tables due to rounding, but these did not affect interpretation of results.

Application to clinical practice

It will be interesting to see how well we apply this new information to our clinical practice. The benefits of taking ASA daily are widely accepted by the public.[4] For secondary prevention of cardiovascular events, including stroke and death, ASA has an absolute risk reduction of 5.1% over 4 years. Yet only about 75% of the patients in this study were taking ASA daily, even though they were under the care of cardiovascular specialists.

This leaves us with a few obvious questions. What are the barriers to placing patients such as these on ASA? Will the challenges be even greater for starting them on ramipril? Also, how do ACE inhibitors affect the benefit of other drugs commonly used for patients with cardiovascular disease? Some studies have suggested that the benefits of ASA and ACE inhibitors are smaller when they are used in combination. Although this study's subgroup analysis suggested that benefit was observed whether or not patients were also taking ASA, specific results were not reported. Does the dose of ASA matter? Did use of β-blockers confer additional benefits?

The findings of this study lend further support to the idea that a disturbance in function of the renin-angiotensin-aldosterone system is probably an independent risk factor for cardiovascular disease. This speculation is made because it makes sense on a molecular level and because improvements in cardiovascular disease far exceed the benefits that accrue from blood pressure reduction alone. As we saw in the recent Randomized Aldactone Study Investigators trial,[5] modifying the renin-angiotensin-aldosterone system appears to encourage vascular remodeling. Since some hypothesize that spironololactone does a better job at suppressing the renin-angiotensin-aldosterone system than ACE inhibitors, it would be interesting to see what effect spironolactone[6] has on patients similar to those in this study.

It is also intriguing that there was a significant reduction in onset of new diabetes in this study. Although this is only a surrogate outcome, it adds weight to speculation that there might be an endocrinologic intertwining of some independent risk factors for cardiovascular disease, such as dyslipidemia, diabetes mellitus, and vascular tissue damage, when the function of the renin-angiotensin-aldosterone system is altered.

For applying the results to our own patients, several cautions deserve mention. The dose of ramipril in the study was 10 mg; lower doses might not be as beneficial. It is not clear whether the results of this study can be generalized to other ACE inhibitors because "tissue specificity" might be relevant. Also, we should not extrapolate the results to justify using angiotensin-receptor blockers in patients who do not tolerate ramipril.

The results of this trial are important and should change our medical practice. They give us another way to practise preventive medicine for our patients at risk of cardiovascular and cerebrovascular events. Along with smoking cessation, diet, exercise, lipid lowering, blood-pressure control, ASA therapy, β-blockers, and probably hormone replacement therapy, we now have excellent evidence for using ramipril for secondary prevention of CAD and stroke.

Bottom line

- Ramipril at 10 mg daily was well tolerated and effective for prevention of cardiovascular disease, stroke, and related mortality in patients with diabetes or cardiovascular disease but no evidence of heart failure.
- The benefits of ramipril on the cardiovascular system far exceed those provided by reducing blood pressure alone. Alterations in the renin-angiotensin-aldosterone system are likely an independent risk factor for cardiovascular disease.
- The results of this study expand the indications for ACE inhibitors in our practice. Ramipril should be prescribed for secondary prevention of cardiovascular disease and stroke.

References

1. Smith SC Jr, Blair SN, Criqui MH, Fletcher GF, Fuster V, Gersh BJ. Preventing heart attack and death in patients with coronary disease. Consensus Panel statement of the American Heart Association. *Circulation* 1995;921:2-4.
2. Lip GYH, Gibbs CR. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. *J Am Coll Cardiol* 1999;33:1424-6.
3. Heart Outcomes Prevention Evaluation study investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:154-60.
4. Goldstein RE, Andrews M, Hall WJ, Moss AJ. Marked reduction in long-term cardiac deaths with aspirin after a coronary event. *J Am Coll Cardiol* 1996;28:326-30.
5. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Study Investigators. *N Engl J Med* 1999;341:709-17.
6. Struthers AD. Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure? *Br J Clin Pharmacol* 1999;47(5):479-82.