Prevention of Heart Failure in Patients in the Heart Outcomes Prevention Evaluation (HOPE) Study

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Background—Previous trials in the prevention of heart failure have been restricted to patients with low ejection fraction or hypertension. We assessed an angiotensin-converting enzyme (ACE) inhibitor, ramipril, to prevent the development of heart failure in high-risk patients without known low ejection fraction or heart failure.

Methods and Results—We randomly assigned 9297 patients to receive double-blind ramipril (10 mg daily) or matching placebo for 4.5 years. Death attributable to heart failure, hospitalization for heart failure, initiation of open-label ACE inhibitor for heart failure, or development of typical signs or symptoms of heart failure developed in 951 patients and was associated with a 4.01-fold increase in the risk of death (P<0.0001). The rate of developing heart failure was significantly increased with coronary disease (risk ratio, 2.17), left ventricular hypertrophy (1.47), increasing age (by decade, 1.37), and diabetes (1.36). Ramipril reduced new-onset heart failure rate from 11.5% to 9.0% (relative risk, 0.77; 95% CI, 0.68 to 0.87; P<0.0001). Ramipril consistently reduced heart failure rate both in those with (relative risk, 0.87) and those without an interim myocardial infarction (relative risk, 0.78). Ramipril also reduced the heart failure rate more in patients with baseline systolic pressure above the median (139 mm Hg) (relative risk, 0.67) compared with those below the median (relative risk, 0.91; P=0.024 for interaction of group by treatment).

Conclusion—Ramipril significantly reduces the rate of development of heart failure in patients at high risk of cardiovascular events. (Circulation. 2003;107:1284-1290.)

Key Words: heart failure ■ prevention ■ drugs ■ atherosclerosis ■ trials

Heart failure is presently the commonest cause of hospital admission in patients older than 65 years of age in the United States,1,2 where it has a prevalence of 2 million and an annual incidence of 400,000.3 Globally, atherosclerosis and coronary artery disease are expected to increase across the world in the next 2 decades4,5 as the levels of obesity, diabetes, and hypertension increase. In addition, more patients are surviving acute myocardial infarction but with damaged hearts, and life expectancy is predicted to increase.4 Therefore, the individual, community, health care, and economic burden of heart failure will continue to rise.

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Once diagnosed, heart failure can have a 1-year mortality as high as 20% to 50%.6–10 Coronary artery disease and hypertension account for most heart failure cases,10,11 but despite major improvements in the detection and treatment of these conditions, heart failure incidence, morbidity, and mortality remain high.6 Angiotensin-converting enzyme (ACE) inhibitors have been proven to reduce morbidity and mortality in patients with low ejection fraction with and without heart failure.12–16 However, there are no data on the impact of ACE inhibitors on heart failure and the outcomes in patients without preexisting heart failure, low ejection fraction, or hypertension. Based on subgroup analysis of previous studies12,13,15,16 and several proposed mechanisms of action,17 the potential for the ACE inhibitor ramipril to reduce mortality and morbidity in patients at high risk of cardiovascular events but without heart failure or known low left ventricular ejection fractions was prospectively evaluated in the Heart Outcomes Prevention Evaluation (HOPE) study.18 The study was discontinued where there was clear and overwhelming evidence of a beneficial effect of ramipril on the primary outcome of the composite of myocardial infarction, stroke, or death from cardiovascular causes. Heart failure, a predefined outcome, was also significantly reduced by 23%.

In this study, we report in detail the predictors of heart failure within the HOPE cohort of patients, the impact of ramipril to prevent heart failure in patients at high risk of cardiovascular events, and the magnitude of benefit in relevant subgroups.
Methods

The HOPE study was a double-blind, placebo-controlled, randomized trial with a two-by-two factorial design conducted to evaluate the effects of ramipril and vitamin E in 9541 patients at high risk of cardiovascular events enrolled at 267 centers in 19 countries from Europe and the Americas. Men and women who were at least 55 years old were eligible if they had a history of coronary artery disease, stroke or peripheral vascular disease, or diabetes plus one other cardiovascular risk factor (hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol level, cigarette smoking, or documented microalbuminuria). Patients were excluded if they had a history of heart failure, were known to have a low left ventricular ejection fraction <0.40, were taking an ACE inhibitor, had uncontrolled hypertension or overt nephropathy, or had a myocardial infarction or stroke within 4 weeks before entering the study. Of these patients, 244 were randomly assigned to receive only low-dose ramipril, 2.5 mg per day as part of a prospective substudy.19 We report the results of 9297 patients randomly assigned to receive ramipril 10 mg once per day or matching placebo. Additional details of the study design and methods have been reported previously.20

The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes and was significantly reduced by 22% in the ramipril group.18 Hospitalization for heart failure was a predefined secondary outcome. All heart failure was defined as heart failure causing death, heart failure requiring hospitalization, heart failure requiring open-label ACE inhibition, or development of typical symptoms and signs as determined by the investigator. The first two were independently adjudicated in a blinded fashion by the End-Points Adjudication Committee.

In this large study, it was impractical to mandate left ventricular ejection fraction measurement in all patients. However, echocardiograms were prospectively obtained as a substudy at 3 centers in 496 enrolled patients. Of these patients, 97.4% had a baseline ejection fraction measurement in all patients. However, echocardiograms were prospectively obtained as a substudy at 3 centers in 496 enrolled patients. Of these patients, 97.4% had a baseline ejection fraction of 0.40 and 2.6% had an ejection fraction <0.40. Mean left ventricular ejection fraction in the echocardiographic substudy was 58%.22 A subsequent review of the charts of randomized patients showed that ventricular function had been evaluated before randomization in 5193. Of these patients, 4772 (91.9%) were documented to have a normal ejection fraction, only 421 (8.1%) had a low ejection fraction, and none had documented heart failure before randomization. Left ventricular hypertrophy was considered to be present if the sum of the amplitude of S wave in V1 and R wave in V5/V6 exceeded 3.5 mV.

Statistical Analysis

The study was originally designed to follow participants for a mean of 3.5 years. However, before the end of this period, the steering committee (whose members were unaware of any of the results) recommended increasing the duration of follow-up to 5 years to account for the impact of a possible lag before treatment had its full effect. All analyses are intention to treat. Time to first occurrence of outcomes are presented as Kaplan-Meier estimates and compared by treatment group using log-rank statistics. Hazard ratios for treatment effect and 95% confidence intervals were derived using Cox regression, stratified for allocation to the vitamin E arm of the factorial design. Events following development of heart failure or myocardial infarction were analyzed as time-dependent covariates in a Cox regression.

Differences in baseline characteristics or between patients who developed heart failure and those who did not were compared using t tests for continuous variables and χ2 tests for discrete variables. Independent factors that predicted heart failure were selected from known risk factors using Cox regression using a backward elimination technique. Subgroup analyses were conducted with the use of tests for interactions in the Cox regression model.

On March 22, 1999, the monitoring board recommended early termination of the study because of the clear evidence of a beneficial effect of ramipril (consistent crossing of the monitoring boundaries in two consecutive reviews). The data at that time showed a 20% reduction in the relative risk of the primary outcome (95% confidence interval, 12% to 28%; z statistic, −4.5; P<0.001). The cutoff date for all events included in the main analysis was set for April 15, 1999, and final visits were scheduled to be completed by June 30, 1999. Vital status was ascertained for 9535 of the 9541 randomized patients (99.9%) at the end of the study.

Results

Detailed baseline characteristics of the population have been reported previously.20 Briefly, mean age was 66 years, 73% were male, 53% had a previous myocardial infarction, 47% had a history of hypertension, and 38% had a history of diabetes mellitus.

Rate of Heart Failure Development

Any heart failure (composite of heart failure death, heart failure requiring hospitalization, heart failure requiring ACE inhibitor, or any reported heart failure) occurred in 951 patients (10.2% of all randomized patients) during a median follow-up of 4.6 years. The patients with documented left ventricular ejection fraction did not have a lower rate of heart failure occurrence (11.7%) than that seen in the main trial. Development of heart failure was associated with a 4.01-fold (95% confidence interval, 3.42 to 4.71) increase in the rate of death (P<0.0001) (Figure 1) and a 4.35-fold (3.56 to 5.31) increase in the rate of cardiovascular death (P<0.0001). Heart failure occurred in 267 (27.2%) of patients with and 684 (8.2%) of patients without an interim myocardial infarction, resulting in an 8.65-fold (7.44 to 9.07) increased risk of heart failure if a myocardial infarction occurred (P<0.0001). Hospitalization for heart failure occurred in 302 patients for a total of 434 heart failure hospitalizations. Of patients hospitalized with heart failure, 72% were hospitalized once, 24% on 2 to 3 occasions, and 4% on 4 or more occasions.

Relationship of Baseline Characteristics and Heart Failure

The prevalence of baseline characteristics in patients who did or did not develop any heart failure is shown in Table 1. Patients who developed heart failure were significantly older, had a higher body mass index, higher systolic pressure, pulse pressure, and heart rate, and were more likely to have one of the trial indicators of vascular disease or its complications. Baseline characteristics that were independently associated with the development of heart failure are given in Table 2.
For each additional risk factor, the statistical model predicted that heart failure occurrence was increased on average 37% (relative risk, 1.37; 95% confidence interval, 1.32 to 1.42; \( P<0.0001 \)). Some baseline characteristics could be expressed as continuous variables, and their influence on development of all heart failure is shown by quartile in Figure 2. Increasing age, body mass index, systolic pressure, and pulse pressure all significantly increased the rate of heart failure, although the most striking effect was that of age, where the rate more than doubled in patients >72 years of age compared with those <62 years of age. The highest baseline quartile for heart rate was also associated with an increased rate of heart failure (<61 bpm, 10.1%; 61 to 68 bpm, 9.2%; 69 to 76 bpm, 9.5%; 77+ bpm, 12.4% rate of heart failure; \( P<0.0002 \) across quartiles).

There was no significant interaction (\( P=0.4 \)) between coronary artery disease and systolic hypertension in predicting the rate of heart failure development. Using only coronary heart disease, systolic hypertension, and pulse pressure, these factors had 68% explanatory power for future heart failure development.

### Effect of Ramipril on Heart Failure Rate

Allocation of treatment to ramipril significantly reduced the rate of all heart failure by 23% (Figure 3) and the rate of combined cardiovascular death and all heart failure by 24% (Table 3). When analyzed separately, each component of the composite heart failure end point showed benefit in favor of ramipril, although the total number of events for heart failure hospitalization, fatal heart failure, and other reported heart failure was smaller; therefore, the benefit did not reach statistical significance separately. The introduction of angiotensin II antagonists for the treatment of new heart failure was very low in the study, 0.97% in placebo and 0.65% in ramipril groups. In the subgroup of 4775 patients with documented normal left ventricular ejection fractions, the benefits of ramipril were similar to the whole group, with a reduction in the rate of all heart failure by 24% (relative risk, 0.76; 95% confidence interval, 0.64 to 0.89; \( P=0.001 \)), prescription of an ACE inhibitor for heart failure by 29% (0.71; 0.57 to 0.88), hospitalization for heart failure by 15% (0.85; 0.63 to 1.14), death from heart failure by 32% (0.68; 0.32 to 1.47), and combined cardiovascular death and all heart failure by 25% (0.75; 0.65 to 0.86; \( P<0.0001 \)).
The benefits of ramipril in reducing all heart failure were consistent across major relevant subgroups (Figure 4). A significant interaction was observed between baseline systolic pressure and treatment group (P=0.024). Ramipril reduced the rate of all heart failure by 9% (relative risk, 0.91; 95% confidence interval, 0.75 to 1.10) in patients with baseline systolic pressure below the median (139 mm Hg) compared with 33% (relative risk, 0.67; 0.57 to 0.80) in patients with baseline systolic pressure at or above the median. There was no interaction between vitamin E and ramipril on the rate of heart failure development.

Effects of Ramipril in Patients With and Without a Myocardial Infarction During the Study

Patients who had myocardial infarction during the study (n=1029) were at increased relative risk of developing heart failure. Ramipril favorably reduced the rate of heart failure after myocardial infarction by 13% (relative risk, 0.87; 95% confidence interval, 0.66 to 1.15) (Figure 5A). Ramipril also significantly reduced the rate of heart failure by 22% in the much larger group of patients (n=8315) who did not have an interim myocardial infarction (relative risk, 0.78; 95% confidence interval, 0.62 to 0.97) (Figure 5B).

Discussion

ACE inhibitors have been shown to reduce mortality across a broad range of patients with chronic symptomatic systolic heart failure attributable to left ventricular systolic dysfunction,7,15 to reduce recurrent episodes of heart failure in patients with acute heart failure or significant left ventricular systolic dysfunction after an acute myocardial infarction,12–14 and to reduce the development of symptomatic heart failure in patients with asymptomatic left ventricular systolic dysfunction.16 The present results with ramipril extend additionally the benefits of ACE inhibition to an even broader range of patients at high risk of cardiovascular events but without a history of heart failure or known left ventricular ejection fraction <0.40. Because ramipril has also been shown to reduce the rates of death, myocardial infarction, and stroke in this population,18 the additional benefits in reducing the rates of heart failure strongly support its role in broad-based cardiovascular protection in high-risk patients. By intention to treat analysis, treating 40 such patients for 4.5 years would prevent 1 new episode of heart failure, including that associated with hospitalization or death. These benefits are mostly additional to the already-reported reduction in cardiovascular death, myocardial infarction, and strokes as well as revascularization procedures. Taking all events into account, treating 13 patients prevents 1 of the above important clinical outcomes.

Heart failure as an outcome was included if it was severe enough to cause withdrawal of study drug to introduce open-label ACE inhibitor, to be the direct cause of a hospital admission, or to be attributed as the cause of death. These reasons accounted for 97% of all recorded episodes of heart failure. The reported results may underestimate the benefits of ramipril to prevent less-severe episodes of heart failure. Only heart failure hospital admissions or heart failure death were independently adjudicated in a blinded fashion by the End-Points Adjudication Committee. The number of these adjudicated events represented 37% of all predefined heart failure events. The clinical relevance and importance of all heart failure events in our study is emphasized by the associated high total mortality (4.0-fold increase) and high cardiovascular mortality (4.4-fold increase). The risk of developing heart failure was not likely to be increased by the inadvertent inclusion of patients with poor left ventricular function at study entry, because the results were consistent in the large subgroup of 4772 patients with documented pre-
served ventricular function. The specific contributions of systolic and diastolic dysfunction were not recorded as measurement of left ventricular ejection fraction, and diastolic filling patterns were not required within the protocol.

We found that the subsequent risk of heart failure was increased 8- to 9-fold after myocardial infarction. Reducing the rate of myocardial infarction will have reduced the left ventricular damage that clearly predisposes to episodes of heart failure. In the patients who did have a myocardial infarction during the study, the risk of subsequent heart failure was reduced, consistent with previous trials of ACE inhibitors. In most patients who did not have an interim myocardial infarction, the results showed a significant beneficial effect of ramipril to prevent heart failure. Seventy-two percent of all heart failure occurred in this group, consistent with a high population-attributable risk. Hence, treatment with ramipril in this group will be expected to prevent more heart failure events than those prevented simply by reducing the rest of myocardial infarctions. In these patients, other risk factors for heart failure, such as hypertension and diabetes, may have played a role. The results demonstrated a significant interaction between ramipril treatment and baseline systolic pressure. The risk of developing heart failure ranged from 12.3% to 9.1% between the highest to the lowest quartile of baseline systolic pressure, and ramipril significantly reduced the rate of heart failure by 33% versus 9% in patients with baseline systolic pressure above or below the median. Diabetes was more prevalent in patients developing heart failure, and ramipril reduces the risk of complications related to diabetes and of diabetes itself.

| TABLE 3. Incidence of Heart Failure and Influence of Ramipril |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Placebo, % (n=4652) | Ramipril, % (n=4645) | RR (95% CI) | P                |
| All heart failure              | 11.5             | 9.0              | 0.77 (0.68 to 0.87) | <0.0001         |
| ACE-I for heart failure*       | 7.0              | 5.2              | 0.72 (0.61 to 0.85) | <0.0001         |
| Heart failure hospitalization* | 3.5              | 3.0              | 0.87 (0.69 to 1.09) |                |
| Fatal heart failure*           | 0.6              | 0.5              | 0.88 (0.51 to 1.53) |                |
| Heart failure signs and symptoms† | 2.6            | 2.5              | 0.95 (0.74 to 1.23) |                |
| Cardiovascular death plus all heart failure | 17.4          | 13.4             | 0.76 (0.69 to 0.84) | <0.0001         |

RR indicates relative risk; CI, confidence interval.
*All patients with this outcome are included.
†Excludes patients who had ACE-I use, heart failure hospitalization, or fatal heart failure.

Figure 4. Relative risk of ramipril versus placebo on selected characteristics. BP indicates blood pressure; Hypert, hypertension; CAD, coronary artery disease; MI, myocardial infarction; LVEF, left ventricular ejection fraction; and BB, β-blocker.
ACE inhibition on the myocardium or vasculature to reduce hypertrophy, atherosclerosis progression, plaque rupture, thrombotic/fibrinolytic balance, or other mechanisms may also have played a role and require additional study.

The echocardiographic substudy of HOPE included baseline and study-end examinations and showed decreased left ventricular end-systolic and end-diastolic volumes and improved left ventricular ejection fraction in the ramipril versus the placebo group. These findings persisted after controlling for BP changes and support a broad beneficial effect of ACE inhibition on left ventricular remodeling.

A limitation of the study design is the inclusion of a small percentage of patients who, on comprehensive chart review, had left ventricular ejection fraction <0.40, but none had documented heart failure symptoms. These patients did not change the overall results, as repeat analysis excluding them still showed the same significant reduction in the rate of heart failure development. Although a preserved left ventricular ejection fraction of >0.40 by itself would not exclude the possibility of diastolic dysfunction at baseline, those patients also would not have been entered into the trial if they had previous symptoms consistent with heart failure. Arm systolic blood pressure was recorded, usually by a nurse or study coordinator, on one occasion as baseline arterial pressure using a standardized protocol in duplicate after the patient had been recumbent for 5 minutes. Treatment with ramipril was well tolerated but was associated with an increase in cough (7.3% versus 1.8%) and a small increase in hypotension or dizziness (1.9% versus 1.5%) requiring discontinuation of double-blind treatment. The percentage of patients who were receiving ramipril 10 mg was 82.9% at 1 year and 62.4% at 4 years.

The benefits of ramipril to reduce the rates of heart failure were consistent in all important subgroups, including patients >65 years of age, females, and patients without known hypertension or diabetes at baseline and were independent of concomitant baseline use of aspirin, diuretics, or β-blockers.

In a previous analysis of SOLVD, a reduced effect of the ACE inhibitor enalapril was observed in those taking anti-platelet agents, although this had not been a predefined interaction. Also, patients in SOLVD were different from those in HOPE, because all had a low left ventricular ejection fraction <0.35 and all patients in the treatment trial had symptoms of heart failure before randomization. The results of our study broaden the cardiovascular protection and use of ramipril to a population of high-risk patients with vascular disease or diabetes plus at least one other cardiovascular risk factor, but without heart failure or known low left ventricular ejection fraction, and undergoing concomitant medical therapy. This study is the first to show that an ACE inhibitor can prevent heart failure in these patients. The prevention of heart failure in this population will reduce the high burden of mortality, morbidity, hospitalizations, and associated costs.

Acknowledgments

Funded by the Medical Research Council of Canada, Hoechst-Marion Roussel, Astra-Zeneca, King Pharmaceuticals, Natural Source Vit E Association and Negema, and the Heart and Stroke Foundation of Ontario.

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_Circulation_. 2003;107:1284-1290; originally published online February 24, 2003;
doi: 10.1161/01.CIR.0000054165.93055.42

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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