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Circulation 2001;104:522-526
DOI: 10.1161/hc3001.093502

Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231
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Effects of Ramipril on Coronary Events in High-Risk Persons
Results of the Heart Outcomes Prevention Evaluation Study

Gilles R. Dagenais, MD; Salim Yusuf, FRCP, DPhil; Martial G. Bourassa, MD; Qilong Yi, MSc; Jackie Bosch, MSc; Eva M. Lonn, MD; Simon Kouz, MD; John Grover, MD; on behalf of the HOPE Investigators

Background—In trials of patients with left ventricular dysfunction or heart failure, ACE inhibitor use was unexpectedly associated with reduced myocardial infarction (MI). Using the Heart Outcomes Prevention Evaluation (HOPE) trial data, we tested prospectively whether ramipril, an ACE inhibitor, could reduce coronary events and revascularization procedures among patients with normal left ventricular function.

Methods and Results—In the HOPE trial, 9297 high-risk men and women, ≥55 years of age with previous cardiovascular disease or diabetes plus 1 risk factor, were randomly assigned to ramipril (up to 10 mg/d), vitamin E (400 IU/d), their combination, or matching placebos. During the mean follow-up of 4.5 years, there were 482 (10.4%) patients with clinical MI and unexpected cardiovascular death in the ramipril group compared with 604 (12.9%) in the placebo group [relative risk reduction (RRR), 21% (95% CI) (11,30); P < 0.0003]. Ramipril was associated with a trend toward less fatal MI and unexpected death [4.0% versus 4.7%; RRR, 16% (~3, 31)] and with a significant reduction in nonfatal MI [5.6% versus 7.2%; RRR, 23% (9,34)]. Risk reductions in MI were documented in participants taking or not taking β-blockers, lipid lowering, and/or antiplatelet agents. Although ramipril had no impact on hospitalizations for unstable angina [11.9% versus 12.2%; RRR, 3% (~9,14)], it reduced the risk of worsening and new angina [27.2% versus 30.0%; RRR, 12% (5,18); P < 0.0014] and coronary revascularizations [12.5% versus 14.8%; RRR, 18%; (8,26) P < 0.0005].

Conclusions—In this high-risk cohort, ramipril reduced the risk of MI, worsening and new angina, and the occurrence of coronary revascularizations. (Circulation. 2001;104:522-526.)

Key Words: myocardial infarction • angina • revascularization • coronary disease • angiotensin

There is evidence that activation of the renin-angiotensin-aldosterone system may increase the risk of acute ischemic heart disease.1 In 3 large trials conducted in patients with heart failure or left ventricular dysfunction (LV), long-term ACE inhibitor (ACE-I) use reduced cardiac mortality and hospitalizations for congestive heart failure and unexpectedly decreased the incidence of acute myocardial infarction (MI).2,3 In one study, ACE-I reduced the occurrence of unstable angina,2 but this observation was not confirmed.6 The Heart Outcomes Prevention Evaluation (HOPE) study extended the benefits of an ACE-I, ramipril, to high-risk persons without known heart failure or LV dysfunction.7 In this trial involving 9247 participants at high risk for cardiovascular (CV) events, ramipril reduced the risk of CV death, nonfatal MI, and strokes. The present report expands these observations by providing greater details on a broad range of coronary events including fatal and nonfatal MI, types of MI, unexpected death, unstable angina, worsening and new angina, and coronary revascularizations.

Methods
The HOPE study was designed as a large, simple, double-blind, randomized trial with a 2×2 factorial design, evaluating the effects of an ACE-I, ramipril, and an antioxidant, vitamin E, their combination, or equivalent placebos on CV events in a high-risk group during a 5-year follow-up.7 However, the study was stopped after a mean follow-up of 4.5 years by the independent monitoring board because of a clear benefit of ramipril on cardiovascular outcomes. Details of the HOPE trial design have been published,7,8 and are briefly outlined.

Study Population
The participants in the HOPE trial were recruited over a period of 18 months from 129 centers in Canada, 27 in the United States, 76 in 14 European Western countries, 30 in Argentina and Brazil, and 5 in Mexico. Participants had to be ≥55 years of age, with documented ischemic heart disease, nondebilitating stroke or peripheral arterial
disease, or diabetes associated with at least 1 of the following risk factors: current cigarette smoking, blood cholesterol >5.2 mmol/L, HDL-cholesterol <0.9 mmol/L, systolic blood pressure >160 mm Hg, diastolic blood pressure >90 mm Hg, or microalbuminuria.

The main exclusion criteria were current use or hypersensitivity to an ACE-I or vitamin E; known left ventricular ejection fraction <0.40; congestive heart failure, acute MI, unstable angina, or multivessel percutaneous coronary intervention (PCI) occurring <1 month before enrollment; or multivessel coronary bypass graft surgery (CABG) done <4 years before entry. In addition, patients with renal dysfunction, uncontrolled hypertension, or other major illness that might interfere with the outcomes were excluded.

The protocol was approved by each institution’s review board or ethics committee. All participants provided written informed consent.

Baseline Measurements, Random Assignment, and Follow-Up
At entry, trained nurses at the different centers interviewed each participant, who answered a standardized questionnaire on medical history, current CV symptomatology, medications, and cardiovascular surgical therapy. Blood pressure and heart rate were measured after a 5-minute rest period in the supine position at baseline and at 1 month, 2 years, and at the final study visit. A urine specimen was tested for the presence of microalbuminuria. A resting ECG was obtained at baseline and at 2 and 4 years of the follow-up. Before random assignment, all eligible participants entered a run-in phase, during which 2.5 mg ramipril was administered daily for 7 days followed by a matching placebo for 10 to 14 days. Among the 9541 participants who met the inclusion criteria, were compliant, and did not have significant side effects, 9297 were randomly assigned to receive 10 mg ramipril once daily or a matching placebo; 244 were randomly selected to receive 2.5 mg ramipril as part of the Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE) substudy and are not included in the present report. After random assignment, participants were allocated daily to 2.5 mg ramipril once per day for 1 week, followed by 5 mg once per day for 3 weeks, and subsequently 10 mg or matching placebo once daily. After random assignment, the follow-up visits were scheduled at 1 and 5 months later and every 6 months thereafter.

Main Outcomes
The diagnosis of MI was based on at least 2 of the following 3 criteria: typical symptoms, elevation of serum cardiac enzymes to twice the upper limit of normal, or diagnostic ECG criteria for Q-wave MI. Silent MI were initially identified by the investigators and confirmed by the Events Adjudication Committee members. Fatal MI was defined as death occurring within 7 days of the acute event. Unexpected death was defined as death occurring within 24 hours of the onset of symptoms without clinical or postmortem evidence of other cause. Unstable angina was defined as new and worsening angina requiring hospitalization. To identify presumed high-risk patients having unstable angina, the following subgroups were analyzed: (1) patients with new ECG ST-segment or T-wave changes and (2) patients with these ECG changes and revascularizations within 7 or 30 days of the events or hospitalized for ≥4 days. All outcome reports were reviewed by an Events Adjudication Committee blinded to treatment; the only exception was the ST- and T-wave changes associated with hospitalization for unstable angina, reported by the investigators. New and worsening angina, whether hospitalized or not, and increased antianginal medication as reported by the investigators were also analyzed. All coronary revascularizations (PCI or CABG) were also documented. The impact of ramipril on coronary events was also analyzed in various subgroups.

Statistical Analyses
The percentage reduction in events is presented as risk reductions [(1−RR)×100], RR being the measured relative risk of an event in the ramipril group in comparison to the placebo group. RR was estimated by Cox regression model stratified according to random assignment to vitamin E or placebo to account for factorial design. Cox regression analyses were done to determine the uniformity of treatment effects across subgroups (age, previous CV events, diabetes, other risk factors, and treatment), and potential interactions between ramipril and each of these factors were examined by incorporating a cross-term into the model. Survival curves were estimated by the Kaplan-Meier procedure.

Results
Baseline characteristics of the study population have been described previously. Briefly, among the 9297 participants with a mean age of 65.9 years, 26.7% were women, 80.6% had a previous coronary event, 43.4% had peripheral artery disease, 10.8% had a previous stroke or transient ischemic attack, and 38.3% had diabetes mellitus. A history of hypertension was documented in 46.5% and dyslipidemia in 65.8%. At entry in the trial in 1993, 76.3% of the participants were taking an antiplatelet agent, 28.9% a lipid-lowering agent, 39.5% a β-blocker, 47.0% a calcium channel blocker, and 15.1% a diuretic.

Myocardial Infarction and Fatal Acute Ischemic Heart Disease
During the mean 4.5 years of follow-up, there were 482 (10.4%) patients with clinical MI and unexpected CV deaths in the ramipril group compared with 604 (12.9%) in the placebo group (RRR of 21%, 95% CI of 11 to 30; P<0.0003). The Kaplan-Meier curves showing the cumulative fatal and nonfatal MI began to diverge after 2 years, and the divergence continued thereafter throughout the follow-up (Figure 1). Patients in the ramipril group had reduced relative risk of nonfatal MI (RRR of 23% (9.34); P<0.0019), either Q-wave MI (18% (−9.38)) or non–Q-wave MI (24% (8.37)). There was a consistent but nonsignificant reduction in fatal MI and unexpected death (RRR, 16% (−3.31); P=0.09) as well as periprocedural MI (16% (−3.31); P=0.09) (Table). A similar trend was observed for silent MI. However, when participants with Q-wave silent and non–silent MI were combined, ramipril reduced the relative risk by 23% [2.5% versus 3.2%; (2.40); P=0.03]. The effect of ramipril was consistent in the various subgroups examined (Figure 2). In particular, consi-
tent results were observed among those on other treatments known to reduce the risk of MI, such as antiplatelet agents [14% (1,24)], lipid-lowering agents [24% (3,41)], and β-blockers [16% (0,30)].

Unstable Angina

Figure 3 illustrates the cumulative incidence of unstable angina according to treatment allocation. No difference was apparent. To find out whether the lack of difference was due to different definitions related to high-risk participants with unstable angina, we explored the effects of ramipril by using various diagnostic criteria. There was no significant impact of ramipril on unstable angina–associated ST-segment or T-wave changes, nor on unstable angina followed by coronary revascularization within 7 or 30 days, nor on unstable angina requiring >4 days of hospitalization (Table).

New and Worsening Angina

There was a significant treatment effect on new and particularly worsening angina [12% (5,18)] (Table). Figure 4 illustrates the new and worsening angina rates among the ramipril and placebo participants. The benefit of ramipril began at the 7th month and was maintained throughout the follow-up. The benefit was observed whether the patients were taking anti-platelet agents 12% (4,19)], β-blockers [11% (1,20)], and to a lesser degree, lipid-lowering agents [12% (~2, 23)].

Coronary Revascularizations

There were 550 and 791 participants who underwent PCI and CABG procedures, respectively. In comparison to placebo, ramipril was associated with a significant lower rate of coronary revascularization procedures [18% (8,26)] (Table). Figure 5 illustrates the rates of revascularization procedures among the participants allocated to ramipril and those allocated to placebo. After ~6 months of follow-up, the rate of revascularizations began to be lower in the ramipril group, and the difference between the two groups increased during the follow-up. The benefit of ramipril was documented in participants taking antiplatelet agents [12% (4,19)], β-blockers [11% (1,20)], and lipid-lowering agents [12% (3,19)].

Discussion

Long-term ramipril reduced the risk of MI, new and worsening angina, and coronary revascularization procedures but had no impact on unstable angina in the high-risk HOPE population. The beneficial effects were documented in addition to other effective therapies.

In previous trials of patients with reduced LV ejection fraction or with heart failure with or without MI, ACE-I decreases the relative risk of MI by a mean of 23% (11,32).2-5 This finding was somewhat unexpected, although it was a prespecified secondary hypothesis. Moreover, among patients with LV dysfunction or heart failure, there is marked activation of the renin-angiotensin-aldosterone system.11 Thus, it is unclear whether the findings documented in LV dysfunction or heart failure can be applied to patients with preserved systolic function and no sign of heart failure. The HOPE trial expanded the observations from these previous trials to high-risk persons with known preserved LV ejection fraction and without known heart failure. The large number of high-risk persons in the HOPE trial and the long-term period of follow-up allowed for the detection of a clear treatment effect on major ischemic outcomes. There was a 21% highly significant reduction in total MI, which was mostly the result of nonfatal MI. There was no evidence of heterogeneity in the different MI presentation reduction, 16% in fatal MI and 26% in other MI types. The beneficial impact of
ramipril on the occurrence of MI was observed in those taking or not taking antiplatelet agents, lipid-lowering agents, and/or β-blockers, indicating that the effects are independent and additive to these agents. Studies targeting the same objectives and high-risk persons with preserved LV function are limited to 1 small cohort, although there are 2 large trials (Prevention of Events with Angiotensin-Converting Enzyme [PEACE] and EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease [EUROPA]) in progress. In the MacMahon et al study, 617 patients with baseline characteristics similar to the HOPE participants were randomly assigned to ramipril or placebo. The patients allocated to ramipril, in comparison to those allocated to placebo, had a risk reduction of the combined outcomes, cardiac death, and MI of 24% (22 of 308 versus 33 of 309) (−14.61). However, this trial did not have the power and was not designed to assess the effects of treatment on these outcomes.

If an ACE-I reduced the risk of MI and new or worsening angina, why did ramipril not lower the rate of unstable angina? We have no definite explanation for this apparent inconsistent observation. In the combined Studies Of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials, hospitalization for unstable angina was documented in 499 (14.7%) patients allocated to enalapril and in 595 (17.5%) in the placebo group [RRR, 20% (9.29)]. Focusing on events requiring hospitalizations for unstable angina associated with ECG changes even with early revascularizations or prolonged hospitalization, we did not observe any significant treatment effect. However, the numbers of events in these specific subgroups are small, and the 95% CI are wide. Therefore, our results cannot completely exclude a 10% to 15% decrease in the relative risk of unstable angina by

**Effects of Ramipril on Coronary Events and Revascularizations**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Events (%)</th>
<th>% Risk Reduction (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total MI</td>
<td>482 (10.4)</td>
<td>21 (11, 30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>604 (12.9)</td>
<td>23 (9, 34)</td>
<td>&lt;0.0019</td>
</tr>
<tr>
<td>Nonfatal Q-wave MI*</td>
<td>90 (1.8)</td>
<td>18 (−9, 38)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal non–Q-wave MI*</td>
<td>109 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal MI</td>
<td>237 (5.1)</td>
<td>24 (8, 37)</td>
<td></td>
</tr>
<tr>
<td>Fatal MI*</td>
<td>155 (3.3)</td>
<td>19 (−2, 36)</td>
<td></td>
</tr>
<tr>
<td>Unexpected death*</td>
<td>13 (0.3)</td>
<td>1 (−114, 54)</td>
<td></td>
</tr>
<tr>
<td>Presumed fatal MI*</td>
<td>59 (1.3)</td>
<td>26 (−9, 50)</td>
<td>0.13</td>
</tr>
<tr>
<td>Other MI</td>
<td>40 (0.9)</td>
<td>28 (−16, 56)</td>
<td></td>
</tr>
<tr>
<td>Silent MI*</td>
<td>155 (3.3)</td>
<td>19 (−2, 36)</td>
<td></td>
</tr>
<tr>
<td>Periprocedural MI*</td>
<td>40 (0.9)</td>
<td>28 (−16, 56)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>554 (11.9)</td>
<td>3 (−9, 14)</td>
<td>0.64</td>
</tr>
<tr>
<td>With ECG ST-T changes*</td>
<td>175 (3.8)</td>
<td>4 (−19, 22)</td>
<td></td>
</tr>
<tr>
<td>With ECG ST-T changes and revascularizations &lt;7 d*</td>
<td>46 (1.0)</td>
<td>3 (−46, 35)</td>
<td></td>
</tr>
<tr>
<td>With ECG ST-T changes and revascularizations &lt;30 d*</td>
<td>51 (1.1)</td>
<td>6 (−38, 36)</td>
<td></td>
</tr>
<tr>
<td>With hospital stay &gt;4 d*</td>
<td>414 (8.9)</td>
<td>0 (−15, 13)</td>
<td></td>
</tr>
<tr>
<td>New or worsening angina</td>
<td>1263 (27.2)</td>
<td>12 (5, 18)</td>
<td>&lt;0.0014</td>
</tr>
<tr>
<td>New angina</td>
<td>1394 (30.0)</td>
<td>12 (5, 18)</td>
<td></td>
</tr>
<tr>
<td>Worsening angina*</td>
<td>262 (5.6)</td>
<td>3 (−15, 19)</td>
<td></td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>1222 (26.3)</td>
<td>12 (4, 18)</td>
<td></td>
</tr>
<tr>
<td>PCI*</td>
<td>292 (6.3)</td>
<td>12 (−3, 26)</td>
<td></td>
</tr>
<tr>
<td>CABG*</td>
<td>439 (9.4)</td>
<td>21 (9, 31)</td>
<td></td>
</tr>
</tbody>
</table>

*All patients with this outcome are included.
†P values were calculated with use of the log-rank test.

**Figure 5.** Kaplan-Meier estimates of cumulative rates of percutaneous and surgical coronary revascularizations in ramipril group and placebo group.
ramipril. It should be emphasized that the SOLVD trials were done between 1985 and 1990 at 83 hospitals linked to 23 centers in the United States, Canada, and Belgium. The HOPE trial was done between 1994 and 2000, in 267 centers in 19 countries. The uses of aspirin and \( \beta \)-blockers were 46.4\% and 17.8\%, respectively, in the SOLVD trials\(^2\) but much more in the HOPE trial (76.3\% and 39.5\%, respectively).\(^3\) Furthermore, it is likely that the practice patterns in the countries of the two studies were very different. It is thus possible that the physicians from the 19 countries in the HOPE trial had various thresholds for hospitalization of worsening angina or new angina. This reflects that the definition of unstable angina based primarily on symptoms was a soft end point, whereas the criteria used for MI, strokes, or death were based on objective and verifiable information. Thus, although we do not have an obvious reason why ramipril had no impact on unstable angina, it is possible that the subjective and variable definition of this event, the practice patterns in different regions, and the play of chance might have contributed to this apparently inconsistent finding in the HOPE trial. The Survival and Ventricular Enlargement (SAVE) trial, a long-term randomized study done in 2231 post-MI patients, also did not observe any reduction in unstable angina, although a significant decrease was documented in mortality rates and MI.\(^4\)

In the HOPE trial there were 2657 participants with worsening angina and new angina, including unstable angina. The occurrence of these events was significantly lowered in the participants allocated to ramipril compared with those allocated to placebo. Although no objective measurements of myocardial ischemia were done, the findings based on the investigators’ observations for lower rates for additional antianginal medication prescribed and fewer revascularization procedures support the possibility that ramipril reduces ischemic cardiac manifestations.

There were fewer participants allocated to ramipril who underwent CABG or PCI as compared with those allocated to placebo. This finding is similar to the results of the SAVE trial.\(^5\) Although the different centers participating in the trial were university and regional hospitals, medical centers, and offices, revascularization centers were accessible for all. In most countries, particularly Canada, where 60\% of the participants came from, patients did not have to pay for this procedure.

ACE-I have traditionally been considered primarily as an antihypertensive medication and subsequently have been shown to reduce preload, afterload, and neurohumoral factors associated with heart failure. Recent data indicate that ACE-I may have an effect on the vascular wall in reducing endothelial dysfunction, decreasing angiotensin II vascular smooth muscle growth and proliferation, diminishing macrophage deleterious effects, having probable antioxidant effects, and affecting thrombogenesis by inhibition of platelet aggregation and enhancement of endogenous fibrinolysis.\(^1\) It is unlikely that the modest blood pressure lowering by ramipril observed in the present study is the sole mechanism for reducing ischemic events among the HOPE participants. The mean blood pressure at entry was 139/79 mm Hg, and ramipril decreased the blood pressure only moderately (mean of 3/2 mm Hg, systolic and diastolic). Adjusting for the blood pressure changes in the trial as time-dependent covariates, the RRR for MI with ramipril did not differ significantly (23% adjusted versus 20% unadjusted). Furthermore, benefit was observed even among patients with elevated blood pressure levels as well as those with blood pressure of 120/70 mm Hg (data not shown). It is likely that in addition to the blood pressure effect, the vascular protective effect of ramipril may have contributed in lowering ischemic events by its role on the endothelium, the atherosclerotic process, and/or thrombogenesis. We have shown a reduction in atherosclerosis progression with ramipril by using B-mode carotid ultrasound in a substudy of HOPE, a finding that supports the vascular protective effect of ramipril.\(^1^2\) However, this finding was not confirmed by another trial.\(^1^2\)

In conclusion, in men and women ≥55 years of age, who are at high risk of CV events, ramipril reduces MI, worsening and new angina, and coronary revascularizations. These benefits are in addition to the other beneficial agents such as antiplatelet agents, \( \beta \)-blockers, and lipid-lowering therapy. Therefore, high-risk patients should be considered for treatment with all 4 agents.

**Acknowledgments**

This study was supported by the Medical Research Council of Canada and Aventis Pharma Inc.

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