Long-Term Effects of Ramipril on Cardiovascular Events and on Diabetes
Results of the HOPE Study Extension

HOPE/HOPE-TOO Study Investigators*

Background—We have previously demonstrated that ramipril reduces vascular events and new diagnoses of diabetes when given for a 4.5-year period. However, it is not known whether the benefits are observed in subgroups of patients at varying risk or on other proven therapies and whether the benefits are sustained beyond the current trial. The 2 aims of this investigation were to assess whether the benefits observed during the HOPE trial were (1) maintained after trial cessation during an additional 2.6 years of follow-up and (2) observed in subgroups based on risk and ancillary treatments.

Methods and Results—Of the initial 267 study centers and 9297 patients, 174 centers and 4528 patients agreed to further follow-up. The rates of use of angiotensin-converting-enzyme inhibitors (ACEIs) in the 2 groups (72% ramipril versus 68% placebo) were similar after the end of the trial. During the posttrial follow-up, patients allocated to ramipril had a 19% further lower relative risk (RR) of myocardial infarction (95% confidence interval [CI], 0.65 to 1.01), a 16% lower RR (95% CI, 0.70 to 0.99) of revascularization, and a 34% lower RR of a new diagnosis of diabetes (95% CI, 0.46 to 0.95). Similar RR reductions in vascular events were observed during and after the active phase of the trial, regardless of baseline risk (RR of 0.76, 0.89, and 0.83 for low-, medium-, and high-risk patients, respectively) or ancillary treatments (RR of 0.90 for aspirin, 0.76 for β-blockers, and 0.84 for lipid-lowering medication).

Conclusions—The benefits of ramipril observed during the active period of the HOPE trial were maintained during posttrial follow-up for cardiovascular death, stroke, and hospitalization for heart failure. Additional reductions in myocardial infarction, revascularization, and the development of diabetes were observed during the follow-up phase despite similar rates of ACEI use in the 2 randomized groups. These benefits were consistent regardless of patient risk or ancillary treatments. (Circulation. 2005;112:1339-1346.)

Key Words: prevention ■ cardiovascular diseases ■ diabetes mellitus

Angiotensin-converting enzyme (ACE) inhibitors have been shown convincingly to reduce the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in a wide range of patients, including those with impaired systolic function, heart failure, and vascular disease with preserved ventricular function.1–8 More recently, several trials in heart failure or left ventricular dysfunction have reported sustained posttrial benefits with ACE inhibitors (personal communication with A.S. Hall, 2003).9–13 Similar long-term data in patients with preserved systolic function treated with ACE inhibitors are unavailable.

The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that 4.5 years of treatment with 10 mg daily of ramipril reduced major vascular events, deaths, and new diagnoses of diabetes in those with preserved ventricular function and vascular disease or high-risk diabetes.9 To assess whether the observed benefits were sustained with a longer duration of observation, we extended the study by 2.6 years (HOPE-TOO; HOPE–The Ongoing Outcomes).

The benefits of ACE inhibitors were also confirmed by the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA),5 whereas the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial reported no reduction in CV events in patients with stable coronary artery disease treated with trandolapril.14 Some investigators have interpreted the PEACE trial results as evidence for a lack of benefit from ACE inhibitor therapy in “low-risk” patients.

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A list of the list of investigators who participated in the study extension (HOPE-TOO) is available in the online-only Data Supplement at http://circ.ahajournals.org/cgi/content/full/112/9/1339/DCl.

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1339
with coronary artery disease or those who are receiving other effective therapies. Therefore, we evaluated the effects of ramipril in the HOPE trial and its extension across subgroups defined by risk and among those using other proven drug therapies.

Methods

Study Design and Participants

The rationale, design, and outcomes of the HOPE study have been published previously. In brief, HOPE was a multicenter, double-blind, placebo-controlled trial. The study randomized 9297 patients with vascular disease and/or diabetes without heart failure or known left ventricular dysfunction to treatment with ramipril, 10 mg daily, or placebo. The study had a 2×2 factorial design with further randomization to vitamin E, 400 IU daily, or placebo and examined the effect of both interventions on CV outcomes. Recruitment began in December 1993 and continued through June 1995 in 267 centers. The ramipril/placebo arm of the HOPE study was stopped earlier than planned because of the clear benefits of ramipril in reducing major vascular events. The close-out visits were completed by August 1999. At this time, all participants stopped taking study ramipril/placebo, were informed of the study results, and were advised to use ACE inhibitors. The Steering Committee extended the study to evaluate whether more prolonged treatment with vitamin E could reduce the risk of cancer or CV events. For the vitamin E arm of the study, blinded allocation to the study drug or placebo was continued during the study extension, whereas an open-label ACE inhibitor was prescribed by the treating physician irrespective of the original allocation.

At the conclusion of the main HOPE trial, all study centers were invited to participate in the extension. One hundred seventy-four of the 267 centers agreed to the extension. Ethics committee approval for the extension was obtained at each center. Participants who were alive at each of the participating centers were invited to participate in the extension and to sign a consent form. There were a total of 6786 participants originally randomized at these centers (3393 assigned to ramipril and 3393 to placebo). Of these, 885 participants, 420 in the ramipril group and 465 in the placebo group, had died before the beginning of the extension. An additional 1373 participants, 656 of those originally assigned to ramipril and 717 of those originally assigned to placebo, refused to participate in the study extension. Of the remaining 4528 patients (77% of those alive at the centers participating in the study extension), 2317 in the ramipril group and 2211 in the placebo group agreed to additional passive (i.e., no longer on study drug) follow-up (Figure 1). During the extension, participants were seen for clinic visits every 6 months. At each visit, ACE inhibitor use as well as data on CV outcomes and new diagnoses of diabetes were recorded, and a brief physical examination was conducted.

Study Outcomes

The main objective of the ramipril arm of the HOPE posttrial study extension was to evaluate whether the reduction in risk of major CV events and of new diagnoses of diabetes in patients treated with ramipril during the HOPE trial was maintained with a longer duration of observation. The primary study outcome was the composite of MI, stroke, and death from CV causes. In addition, we evaluated the individual components of this outcome. CV outcomes continued to be adjudicated by an Events Adjudication Committee, blinded to the original treatment allocation. New diagnosis of diabetes was a predefined secondary outcome in the HOPE posttrial extension according to similar criteria as before. Additional objectives included the evaluation of patients defined by risk and by baseline use of other drug therapies known to benefit patients with vascular disease. Baseline risk was computed with a risk model that predicted the probability of sustaining a major vascular event based on age, sex, history of current smoking, hypertension, diabetes, stroke, coronary artery disease, left ventric-
further reduction in major CV events. Of the patients originally allocated to treatment with ramipril, 220 (7.9%) had major CV events compared with 225 (8.4%) of those originally allocated to placebo (relative risk [RR] 0.91; 95% confidence interval [CI], 0.76 to 1.10). There was a further reduction in the risk of MI (146 [5.1%] versus 169 [6.1%]; RR 0.81; 95% CI, 0.65 to 0.97; \( P < 0.0007 \); Table 3 and Figure 3A), fewer strokes (174 [5.1%] versus 215 [6.3%]; RR 0.79; 95% CI, 0.65 to 0.97; \( P < 0.023 \); Table 3 and Figure 3B), and fewer CV deaths (327 [9.6%] versus 374 [11.0%]; RR 0.86; 95% CI, 0.74 to 1.00; \( P < 0.045 \); Table 3 and Figure 3C).

**Other Cardiac Outcomes**

There were fewer revascularizations in the ramipril group during the 2.6 years of extension (235 [9.1%] compared with placebo (259 [10.5%]; RR 0.84; 95% CI, 0.70 to 0.99; Table 2). The combined in-trial and posttrial rates of revascularization were 22.6% compared with 25.9% for placebo (RR 0.84; 95% CI, 0.76 to 0.92; \( P < 0.0003 \); Table 3). The rates of hospitalization for unstable angina [385 [16.6%] in the ramipril group versus 375 [17.0%] in the placebo group) and hospitalization for heart failure (94 [4.1%] in the ramipril
New Diabetes

During the extension only, in those patients who had not developed diabetes by the end of the HOPE study, there was a significant further reduction in risk for diabetes (48 [2.7%] for patients in the ramipril group versus 70 [4.0%] in the placebo group; RR 0.66; 95% CI, 0.46 to 0.95; Table 2).

Considering the combined in-trial period and posttrial follow-up of 7.2 years, there was a 31% RR reduction in new diagnoses of diabetes (152 [7.3%] patients in the ramipril group versus 216 [10.3%] in the placebo group; RR 0.69; 95% CI, 0.56 to 0.85; P=0.0006; Table 3 and Figure 4).

Subgroup Analyses

The beneficial effect of ramipril on the primary composite end point was consistently observed among the subgroups analyzed, in both the main randomized HOPE trial and the HOPE study extension. This benefit was observed in patients at low risk (annual placebo event rate of 1.9%/y, RR 0.76), medium risk (annual placebo event rate of 3.8%/y, RR 0.89), and high risk (annual placebo event rate of 6.0%/y, RR 0.83). The P value for heterogeneity was 0.67, suggesting that the benefits in preventing CV events were similar across a 3-fold range in patient risk. Significant benefits were also observed among those taking aspirin (RR 0.85), β-blockers (RR 0.76), and lipid-lowering drugs (RR 0.84) at the beginning of the trial, either in combination or individually, as well as in those patients not taking these medications (Figure 5).

Discussion

There are 2 new and major findings that are reported here: first, that the benefits observed during the HOPE trial were sustained during passive follow-up. Moreover, there were incremental benefits primarily in reducing not only the
incidence of new diabetes but also the rates of MI and revascularization, despite similar ACE inhibitor use and blood pressure levels between the 2 study groups during the extension period. Therefore, it is likely that the observed benefits of ACE inhibitors at the end of the in-trial period are an underestimate of the benefits of more prolonged treatment. This implies that ramipril may have favorably altered endothelial or vascular structure/function, and that the benefits persisted beyond the period of “contrast” experienced during the blinded phase of the trial. Prevention strategies are likely to be used lifelong, and it is possible that the true benefits of ramipril are greater than those observed at the end of the blinded period.

The use of ACE inhibitors during the extension was similar in the 2 study arms, so that in fact, a strategy of early versus late initiation of ACE inhibitor therapy is being evaluated in the study extension. Therefore, the benefits observed in the study extension data indicate that the 4.5 years of initial, “earlier” use of ramipril therapy provided a longer-term protective effect compared with later initiation. Our findings also indicate that ACE inhibitor therapy favorably influences metabolic processes, leading to substantial reductions in the rates of new diagnoses of diabetes, and these effects are also maintained long term. In fact, the further reduction in MI and diabetes rates observed during the study extension in patients originally allocated to treatment with ramipril suggests that ACE inhibitor therapy may “reset” processes involved in atherosclerosis and glucose metabolism.

During the follow-up period, we did not observe an additional treatment effect for stroke. Blood pressure was similar during the posttrial follow-up and suggests that an important mechanism by which strokes may have been reduced during the blinded part of the study (where there was a modest difference in blood pressure of 3/2 mm Hg) was blood pressure lowering.

Previous studies of long-term posttrial follow-up of patients enrolled in ACE inhibitor trials have evaluated only those with heart failure and/or left ventricular dysfunction. Early initiation of ACE inhibitors in such patients was shown to have sustained long-term benefits in several studies. Data from the extended follow-up of the SOLVD (Studies of Left Ventricular Dysfunction) Prevention trial indicated that for an additional 8.6 years of follow-up after the study end, there was an increase in treatment benefit. During the blinded part of the trial, there was a 12% RR reduction in CV mortality, which increased to a 16% RR reduction in CV mortality after 16 years. Similarly, the AIRE (Acute Infarction Ramipril Efficacy) Study demonstrated that after 15 months of treatment with ramipril (compared with placebo), there was a 27% RR reduction in all-cause mortality. At the completion of 3 years of posttrial follow-up of 603 of the originally randomized 2006 patients, there was an overall 36% RR reduction in favor of treatment.

![Figure 2. Kaplan-Meier estimates of the composite outcome of MI, stroke, or CV death in the ramipril group and the placebo group in the centers continuing in the study extension.](image)

**TABLE 3. Major CV Events and New Diagnosis of Diabetes for the Combined In-Trial and Posttrial Periods**

<table>
<thead>
<tr>
<th>Event</th>
<th>No of Patients (%)</th>
<th>Ramipril (n=3393)</th>
<th>Placebo (n=3393)</th>
<th>RR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, stroke, or CV death</td>
<td></td>
<td>699 (20.6)</td>
<td>820 (24.2)</td>
<td>0.83 (0.75–0.91)</td>
<td>0.0002</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td>485 (14.3)</td>
<td>581 (17.1)</td>
<td>0.81 (0.72–0.92)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>174 (5.1)</td>
<td>215 (6.3)</td>
<td>0.79 (0.65–0.97)</td>
<td>0.023</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td>327 (9.6)</td>
<td>374 (11.0)</td>
<td>0.86 (0.74–1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td>767 (22.6)</td>
<td>880 (25.9)</td>
<td>0.84 (0.76–0.92)</td>
<td>0.0003</td>
</tr>
<tr>
<td>New diagnosis of diabetes</td>
<td></td>
<td>152 (7.3)</td>
<td>216 (10.3)</td>
<td>0.69 (0.56–0.85)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

*P values were calculated by the log-rank test and data on all study participants at centers that participated in the study extension, censored for period of observation.
inhibitors improve endothelial function.18 Our findings suggest that this effect on vascular health leads to long-term improvement in clinical outcomes. Similarly, there is mounting evidence supporting a favorable effect of ACE inhibition on glucose metabolism,20 and our observations in the main HOPE trial and the HOPE extension support the notion that these translate to reduced rates of diabetes. Moreover, substudies of HOPE have demonstrated reduced atherosclerosis progression rates21 as well as lower fasting glucose levels17 in subsets of HOPE study participants treated with ramipril. The results of HOPE and HOPE-TOO may be explained, at least in part, by these vascular and metabolic effects of long-term ACE inhibition.

Collectively, HOPE and the other trials support the concept of sustained, irreversible, and favorable ventricular and vascular remodeling. In addition, enhancement of the impact on prevention of diabetes indicates that sustained blockade of the renin-angiotensin-aldosterone system also results in sustained, favorable effects on glucose homeostasis. The second new observation reported here is related to the consistency of benefits in those at low, medium, and high risk. Similarly, the benefits were observed in those receiving aspirin, β-blockers, or lipid-lowering agents. In the subgroup analysis of ramipril based on baseline use of ancillary treatment, the only statistically significant interaction in effect was noted in the subgroups who were or were not receiving aspirin at baseline. The benefits in those receiving aspirin (RR 0.85) appeared to be smaller compared with those not receiving aspirin (RR 0.62). Nevertheless, the benefits were both statistically and clinically significant in patients who were taking aspirin, suggesting that such patients will derive additional benefit from ramipril. A recent meta-analysis of all available trials support our findings.22

The benefits of ramipril observed in HOPE are additive to those of other proven therapies and are supported by similar results from the EUROPA trial.5 Moreover, in both trials, the RR reduction for the composite primary outcome was similar in patients classified as being at low, intermediate, and high risk (over a 3- or 4-fold range of risk), indicating that most patients with vascular disease are likely to benefit from ACE inhibitors. Although the absolute risk reductions attained with ACE inhibitors were smaller in lower-risk patients during the relatively short duration of the trials, it is likely to be substantial during longer-term therapy, because the lifetime risk of recurrent vascular events or diabetes is high in most patients with vascular disease. Considering the very low risk for major adverse events associated with ACE inhibitors and the proven cost-effectiveness of this therapy,23 ACE inhibitors should be offered to most patients with vascular disease unless they have contraindications.

Study Limitations
Two thirds of the original cohort agreed to continued follow-up. Although complete follow-up on all participants would
have been preferable, the patients at the centers continuing in the study extension appeared to be similar to the entire HOPE study population. Indeed, the baseline characteristics and the in-trial outcomes of the patients at centers continuing in the study extension and those of the entire HOPE study cohort were similar, indicating that there was no obvious bias in the group that agreed to continued follow-up.

Conclusions
The results of the extended follow-up of HOPE participants demonstrate sustained vascular and metabolic benefits attained with ACE inhibitor therapy. This indicates that the reduction in CV outcomes demonstrated at the end of the HOPE study is most likely an underestimate of the full effects of long-term ramipril therapy. Subgroup analyses demonstrate that the benefits observed are additive to those of other life-saving therapies and extend to all patients with vascular disease, independent of their baseline risk. From a clinical perspective, ACE inhibitor therapy should be used in most patients with vascular disease or diabetes and additional CV risk factors. Our study also underscores the need to complete longer-term follow-up of most prevention trials, so that better estimates of the long-term benefits of treatment can be obtained.

Disclosure
Jackie Bosch has served on the speakers’ bureaus of and/or received honoraria from Aventis Pharmaceuticals, King Pharmaceuticals, and Wyeth Pharmaceuticals. Dr Lonn has received research grants from Aventis, Sanofi, and King; has served on the speakers’ bureaus of and/or received honoraria from Aventis, Sanofi, and Wyeth; and has served as a consultant to or on the advisory boards of Aventis, Sanofi, and King. Dr Arnold has received a grant and honoraria from and has served as a consultant to Aventis. Dr Dagenais has received a research grant from Aventis and has received speaker’s fees from Sanofi-Aventis. Dr Yusuf has received research grants and other research support from and has served on the speakers’ bureau of and/or received honoraria from Aventis.

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