Reduction of cardiovascular events and microvascular complications in diabetes with ACE inhibitor treatment: HOPE and MICRO-HOPE

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Summary

The Heart Outcomes Prevention Evaluation (HOPE) study, an international randomized trial, was designed to evaluate the effects of the angiotensin-converting enzyme (ACE) inhibitor ramipril and vitamin E in patients at high risk for cardiovascular events. The study did not detect any cardiovascular benefit or harm using vitamin E. Results for the vitamin E arm are not discussed here. Of 9541 patients, 3577 with diabetes received either ramipril (10 mg) or placebo. Among these patients, ramipril use was associated with a significant 25% reduction in risk for the composite endpoint of myocardial infarction (MI), stroke, or cardiovascular death after a median follow-up period of 4.5 years. This benefit was independent of any blood pressure-lowering effect. The Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE (MICRO-HOPE) substudy in this patient population showed that ramipril treatment was associated with a decreased risk of development of overt nephropathy. Use of a composite measure of microvascular complications also suggested a protective effect of ramipril treatment. An interesting finding in the HOPE study is that ramipril treatment was associated with a significant 34% reduction in new diagnoses of diabetes. The possibility that ACE inhibitor treatment with ramipril may prevent new diabetes in non-diabetic patients at high risk of the disease is to be examined prospectively in the Diabetes Reduction Assessment with ramipril and rosiglitazone (DREAM) trial. Copyright © 2002 John Wiley & Sons, Ltd.

Keywords microalbuminuria; myocardial infarction; nephropathy; ramipril

Introduction

Evidence has suggested that angiotensin-converting enzyme (ACE) inhibition may prevent cardiovascular events. The Heart Outcomes Prevention Evaluation (HOPE) study [1] was conducted to directly test this possibility in patients without heart failure or low ejection fraction who were at increased risk of cardiovascular events. In addition, the trial was designed to recruit almost 4000 people with diabetes.

The rationale for including patients with diabetes, and for using ACE inhibitors in this patient population, has several components. Diabetes is a strong independent cardiovascular risk factor [2–7], and the likelihood of death from cardiovascular causes is two to four times higher in people with diabetes than in people without diabetes. There is also evidence that diabetes is associated with activation of the tissue renin–angiotensin system and higher tissue ACE levels. The observation that ACE inhibitor treatment was associated with reduced end-stage renal disease and diabetic nephropathy in patients with type 1 diabetes suggested that these effects might be due to a cardiovascular benefit in addition to a renal benefit [8]. Moreover, ACE inhibitors may have beneficial metabolic effects. Therefore, an important
objective of the HOPE trial was to assess cardiovascular outcomes in patients with diabetes. The MICRO-HOPE (Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE) substudy was specifically designed to assess the effects of ACE inhibitor treatment on overt nephropathy in patients with diabetes.

**ACE inhibitors and the prevention of cardiovascular disease**

Angiotensin-converting enzyme acts within the renin–kallikrein system both to convert angiotensin I to angiotensin II in tissue and in the circulation and to break down bradykinin. Angiotensin II is a potent vasoconstrictor, with both systemic activity and glomerular efferent arteriolar activity. Angiotensin II also increases adrenal production of aldosterone and is a potent growth factor for smooth muscle, endothelium, and mesangium. Bradykinin is a vasodilator that stimulates endothelial production of nitric oxide (NO) and prostacyclin. Inhibition of ACE activity results in decreased angiotensin II levels and increased bradykinin levels. A decrease in angiotensin II levels causes reductions in blood pressure, myocardial demand, left ventricular mass, smooth muscle cell proliferation, platelet aggregation, and endothelial production of endothelin and plasminogen activator inhibitor-1 (resulting in increased tissue plasminogen activator levels). ACE inhibitor-induced increases in bradykinin result in vasodilatory effects mediated by NO, prostacyclin, and bradykinin; decreased platelet adhesion to the endothelium in association with increased NO; and NO-induced reduction in smooth muscle cell proliferation [9].

Epidemiologic studies have supported the possibility that ACE inhibition could reduce the risk of cardiovascular disease. These studies found that individuals with higher renin profiles were at increased risk of future myocardial infarction (MI), irrespective of other risk factors for cardiovascular disease [10]. In addition, individuals with the ACE DD genotype, which is associated with increased ACE levels, are at increased risk of MI [11]. Evidence of a treatment effect of ACE inhibition in preventing cardiovascular events was provided by clinical trials of ACE inhibitors in patients with heart failure or post-MI left ventricular dysfunction [9]. Follow-up for MI as a secondary endpoint in the trials indicated that in addition to reducing mortality in these patients, ACE inhibitor treatment was associated with a reduction in MI and stroke.

**HOPE trial**

**Design**

The HOPE trial, an international, randomized, double-blind, placebo-controlled 2×2 factorial trial, assessed the effects of the ACE inhibitor ramipril and vitamin E [1,12]. No effect of vitamin E was detected, either beneficial or deleterious. The results for the vitamin E arm are not discussed in this article and have been reported elsewhere. Patients included were at least 55 years of age and were at increased risk for cardiovascular events because of previous cardiovascular disease or because of diabetes mellitus plus at least one other cardiovascular risk factor (i.e., hypertension, hypercholesterolemia or low high-density lipoprotein cholesterol, cigarette smoking, microalbuminuria, or previous cardiovascular disease). In addition, study patients did not have low left-ventricular ejection fraction or heart failure. Patients with urine dipstick proteinuria findings of 1+ or greater were excluded.

**Patient population**

Results in the patient population with diabetes have been reported separately [13]. A total of 3654 patients with diabetes (38% of the total HOPE trial population) were enrolled in the study, and 3577 were randomized to ramipril 10 mg or placebo. An additional 77 were enrolled in the Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE), a HOPE subtrial, and took low-dose ramipril as study drug. The ramipril and placebo groups were well matched for diabetes duration, diabetes treatments, distribution of additional cardiovascular risk factors, blood pressure, and use of medications for cardiovascular disease or cholesterol lowering. The groups were also well matched for baseline glycated hemoglobin level, serum creatinine concentration, and proportion with albumin/creatinine ratio of 2 mg/mmol or greater. Overall, mean age was 65 years and mean duration of diabetes was 11 years. A total of 69% of patients had previous cardiovascular disease, 56% had hypertension, 65% had hyperlipidemia, and 32% had microalbuminuria (albumin/creatinine ratio ≥ 2 mg/mmol). The mean glycated hemoglobin level was 123% above the upper limit of normal.

**Outcomes in patients with diabetes**

The trial was stopped early because ramipril was shown to have a consistent benefit compared with placebo in reduction of cardiovascular events in patients with diabetes [13]. After a median follow-up of 4.5 years, ramipril treatment was associated with a significant 25% reduction in risk of the primary composite outcome measure of MI/stroke/cardiovascular death (Table 1) and with significant reductions in risk of the individual components of cardiovascular death (37%), MI (22%), and stroke (33%) [1]. The significant reduction in all-cause mortality (24%) was attributable to the significant effect in preventing cardiovascular death. Subgroup analysis showed that treatment was associated with consistent benefit among patients with and without microalbuminuria, patients with and without previous cardiovascular disease, patients grouped by diabetes treatment regimen (dietary hyperglycemic control, oral
changes in blood pressure. After controlling for the primary endpoint [relative risk (RR) 0.75, 95% confidence interval (CI) 0.64 to 0.88] after controlling for hyperglycemic agents or insulin, or both), and patients with type 1 and/or type 2 diabetes.

**Microalbuminuria**

A strong relationship between microalbuminuria and cardiovascular risk factors was evident. At baseline, there were a number of significant differences in the profiles of patients with microalbuminuria compared with the profiles of those without microalbuminuria – including increased age, increased duration of diabetes, greater waist/hip ratio, increased systolic and diastolic blood pressure, decreased ankle/arm index, increased serum creatinine, and increased glycated hemoglobin. Independent determinants of microalbuminuria in the patient population included age, blood pressure, cigarette smoking, prior stroke/endarterectomy, prior peripheral vascular disease, increased waist/hip ratio, left ventricular hypertrophy, diabetes duration, insulin use, and elevated glycated hemoglobin level [14].

**Blood pressure**

The benefits of ramipril treatment were independent of its effect on blood pressure [13]. The ramipril patients did have significant decreases compared with placebo in systolic pressure (−1.9 mmHg vs +0.55 mmHg) and in diastolic pressure (−3.3 mmHg vs −2.3 mmHg). By study end, however, multiple regression analysis showed that ramipril was associated with a 25% reduction in risk for the primary endpoint [relative risk (RR) 0.75, 95% confidence interval (CI) 0.64 to 0.88] after controlling for changes in blood pressure.

**Glycated hemoglobin**

Analyses of cross-sectional data indicated that ramipril was associated with lower levels of glycated hemoglobin over the first 2 years of the study compared with placebo [1]. Reported changes consisted of a mean absolute increase above the upper limit of normal of 1.5% versus 3.4% (p = 0.04) at year 1 and a mean decrease of 0.1% versus an increase of 2.2% at year 2. Thereafter, the change in glycated hemoglobin level was similar in the ramipril and the placebo groups.

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### Table 1. Event rates in patients with diabetes in the HOPE trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Ramipril (n=1808)</th>
<th>Placebo (n=1769)</th>
<th>RRR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined primary outcome (MI/stroke/cardiovascular death)</td>
<td>277 (15.3)</td>
<td>351 (19.8)</td>
<td>25% (12–36)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Cardiovascular deathb</td>
<td>112 (6.2)</td>
<td>172 (9.7)</td>
<td>37% (21–51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MIb</td>
<td>185 (10.2)</td>
<td>229 (12.9)</td>
<td>22% (6–36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Strokeb</td>
<td>76 (4.2)</td>
<td>108 (6.1)</td>
<td>33% (10–50)</td>
<td>0.0074</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>196 (10.8)</td>
<td>248 (14.0)</td>
<td>24% (8–37)</td>
<td>0.004</td>
</tr>
</tbody>
</table>


**MICRO-HOPE substudy**

The MICRO-HOPE substudy was designed to determine whether ACE inhibitor treatment reduces progression of early renal disease in patients with diabetes [13]. Patients were screened for nephropathy by assessment for an albumin/creatinine ratio ≥36 mg/mmol at 1 year and at study end and for urine dipstick proteinuria findings of ≥1+ at annual visits during the study. Patients with positive findings on screening underwent 24-h urine collection; nephropathy was diagnosed on the basis of a 24-h urine albumin ≥200 µg/min or ≥300 mg/d or a 24-h urine protein >500 mg/d. Because of the early termination of the trial, 24-h urine collection results were not available in 48 cases of positive screening results; in these cases, an albumin/creatinine ratio ≥36 mg/mmol was used as the diagnostic criterion.

According to these criteria for overt nephropathy, ramipril treatment was associated with a significant 22% reduction in risk of nephropathy (Table 2) [13]. This finding was robust; similar risk reductions were noted when more stringent criteria for nephropathy were applied. Ramipril treatment was also associated with significantly reduced albumin/creatinine ratios compared with placebo. Use of a composite measure for microvascular disease consisting of nephropathy based on the study definition, patient-reported dialysis, and patient-reported laser therapy for retinopathy indicated that ramipril was associated with a significant 15% reduction in risk for microvascular complications.

**ACE inhibitors and prevention of diabetes**

Development of diabetes was not a prespecified outcome in the HOPE trial. However, analysis of patient-reported disease among patients without diabetes at baseline showed that ramipril treatment was associated with a significant 34% reduction in new-onset diabetes (RR 0.66, 95% CI 0.51–0.85) [1].

Although there are a number of potential mechanisms whereby ACE inhibition might prevent diabetes, no consensus exists. Nevertheless, the potential for protective effects and the provocative findings in the HOPE trial...
have helped spur the design of a prospective trial to assess the activity of ACE inhibition in this regard. The DREAM study will assess whether ramipril can prevent new-onset diabetes in at-risk individuals.

Conclusions

The findings of the HOPE study and the MICRO-HOPE substudy indicate that ACE inhibitor treatment with ramipril results in reductions in cardiovascular events and diabetic nephropathy in patients with diabetes and other cardiovascular risk factors. This reduction is independent of the effect of ACE inhibitor therapy on blood pressure. On the basis of these findings, it has been calculated that 15 at-risk patients with diabetes would need to be treated with ramipril for 4.5 years to prevent one patient from having an MI, stroke, cardiovascular death, hospitalization for heart failure, revascularization, overt nephropathy, laser therapy for retinopathy, or renal failure – a number that compares very well with those for other commonly prescribed treatments. In addition, there is provocative evidence from the HOPE trial that ACE inhibitor treatment may prevent the development of diabetes. This hypothesis is to be tested in the prospective DREAM trial.

References


Table 2. Development of overt nephropathy and overall development of microvascular disease in patients with diabetes

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Ramipril</th>
<th>Placebo</th>
<th>RR (95% Cl)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt nephropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h test + ACR</td>
<td>122 (6.8)</td>
<td>151 (8.5)</td>
<td>0.78 (0.62–0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>24-h test only</td>
<td>101 (5.6)</td>
<td>124 (7.0)</td>
<td>0.79 (0.61–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>24-h test + ACR + laser therapy</td>
<td>18 (1.0)</td>
<td>29 (1.6)</td>
<td>0.62 (0.34–1.12)</td>
<td>0.11</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephropathy (24-h test + ACR)</td>
<td>122 (6.8)</td>
<td>151 (8.5)</td>
<td>0.78 (0.62–0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>Laser therapy</td>
<td>170 (9.4)</td>
<td>195 (10.5)</td>
<td>0.88 (0.72–1.09)</td>
<td>0.24</td>
</tr>
<tr>
<td>Dialysis</td>
<td>10 (0.6)</td>
<td>8 (0.5)</td>
<td>1.20 (0.47–3.05)</td>
<td>0.70</td>
</tr>
<tr>
<td>Total microvascular complications</td>
<td>278 (15.4)</td>
<td>314 (17.8)</td>
<td>0.85 (0.72–1.00)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

RR, Relative risk; CI, confidence interval; ACR, albumin/creatinine ratio.